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Vitamin D - Pivotal Nutraceutical in the Regulation of Cancer Metastasis and Angiogenesis

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Abstract: Various epidemiological studies have demonstrated that vitamin D may play important roles in the pathogenesis and progression of cancer. Vitamin D is one of the most pivotal nutraceuticals whose active metabolite, calcitriol (1,25-dihydroxyvitamin D_3), possesses anti-proliferative, pro-apoptotic, and pro-differentiating capabilities. Accumulating evidence indicates that the potential benefits of using vitamin D in cancer are not only anti-cancer cell proliferation which is linked with its anti-inflammatory effects, including the suppression of prostaglandin metabolism and inhibition of NF-κB signaling, but also suppressing tumor metastasis and angiogenesis. Here, we present a systematic summary of the effects of vitamin D in the chemoprevention and chemotherapy of cancer, especially anti-metastatic and anti-angiogenic actions.

Keywords: Angiogenesis, calcitriol, cancer prevention, epidemiology, epithelial-mesenchymal transition, metabolism, metastasis, synthesis, vitamin D, review.

INTRODUCTION

Despite the therapeutic advances, cancer is still the second leading cause of death in the United States, with an estimated 1,638,910 new cases and 577,190 deaths in 2012. The most common fatal cancers are lung, bronchus, prostate, breast and colorectum cancer, which account for approximately half of the total cancer deaths among men and women [1]. Metastasis is responsible for nearly 90% of cancer-related deaths [2]. In recent years, epithelial-mesenchymal transition (EMT), an orchestrated event of cells characterized with a loss of cell-cell adhesion mediated by E-cadherin repression and enhanced cell mobility, has received significant attention in cancer progression. EMT in cancer invasion, metastasis, recurrence, and chemoresistance has been found in a variety of epithelial cancers, such as prostate cancer, breast cancer, lung cancer, gastrointestinal tumors and malignant melanoma [3-4]. In addition, angiogenesis is also a crucial step for cancer progression [5]. The new blood vessels embedded in the tumor not only offer supplies for tumor growth, but also provide an efficient route for tumor cells to enter the blood circulation and to colonize to distant organs, such as liver, lung or even bone. Therefore, therapeutic approaches targeting cancer metastasis and angiogenesis are attractive strategies for the prevention and treatment of cancer.

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A group of nutraceuticals including soy isoflavone, curcumin, tea polyphenols, resveratrol, indole-3-carbinol, lycopene, and vitamin D have been demonstrated to prevent or inhibit the cancer process [6-7], among which vitamin D not only exerts anti-proliferative, pro-apoptotic and pro-differentiating actions in cancer, but also suppresses tumor invasion, metastasis and angiogenesis [8-10]. Vitamin D levels have been regarded as an independent prognostic factor of many cancers [11-12]. In this review, the anti-metastatic and anti-angiogenic actions of vitamin D and its related mechanisms will be discussed.

VITAMIN D SYNTHESIS AND METABOLISM

As a lipid soluble substance, vitamin D belongs to the family of secosteroid hormones. Vitamin D is readily accessible from a few foods and dietary supplements. Dietary vitamin D exists in two forms: vitamin D_2 (ergocalciferol), which is derived from fungi or plant, and vitamin D_3 (cholecalciferol), which is present in animal sources [9]. Skin can also synthesize vitamin D under sunlight exposure. Ultraviolet light with certain wavelength (270-300nm) converts the precursor 7-dehydrocholesterol to the secosteroid vitamin D_3. It is then metabolized in the liver by the enzyme 25-hydroxylase (CYP27A1) to form the prohormone 25-hydroxy vitamin D_3 [25 (OH) D_3]. 25 (OH) D_3 further converts to 1,25$(OH)_2$ D_3 (or calcitriol) in the kidney by 1α-hydroxylase (CYP27B1) afterwards [9,13]. Importantly, CYP27B1 is also expressed in many other tissues, including colon, breast, prostate, lung, pancreas, placenta and various cells of the immune system, to synthesize calcitriol and in-

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duce an autocrine/paracrine action of vitamin D_3 [14-15]. Converting 24-hydroxylation of 25 (OH) D_3 and calcitriol to the metabolites 24,25 $(OH)_2$ D_3 and 1α,24,25$(OH)_2$ D_3 by 24-hydroxylase (CYP24A1) is the rate-limiting step for the catabolism of 25 (OH) D_3 and calcitriol (Fig. **1**) [16].

Vitamin D-Metabolizing Enzymes

The synthesis and degradation of vitamin D are regulated by the enzymes CYP27B1 and CYP24A1 respectively. Lopes *et al.* [17] have shown that CYP27B1 expression is lower in invasive breast carcinomas compared with benign lesions and CYP24A1 expression was elevated in carcinomas than that in benign lesions. McCarthy *et al.* [18] also demonstrated that CYP27B1 mRNA expression was significantly down-regulated in adjacent non-cancerous breast tissue from patients with breast cancer in comparison with that from individuals without breast cancer. The similar results were also observed in colon cancer by Bises and colleagues that high-grade undifferentiated colorectal cancers have a lower expression of CYP27B1 than low grade tumors [19]. These results imply that reduced synthesis or enhanced degradation of vitamin D may be associated with cancer progression.

Retinol X Receptor (RXR) and Vitamin D Receptor (VDR)

Vitamin D binding protein (DBP) (300–600 mg/mL in bloodstream) is the main transporter of vitamin D in the circulatory system [20]. Vitamin D receptor (VDR), which is a member of the steroid hormone receptor superfamily of ligand-activated transcription factors, is a crucial mediator for the cellular effects of vitamin D [21]. The VDR gene is located on chromosome 12q12–q14 and several single-nucleotide polymorphisms including FokI (rs2228570) and BsmI (rs1544410) have been identified that may influence cancer risk [22]. The binding of calcitriol to the nuclear VDR

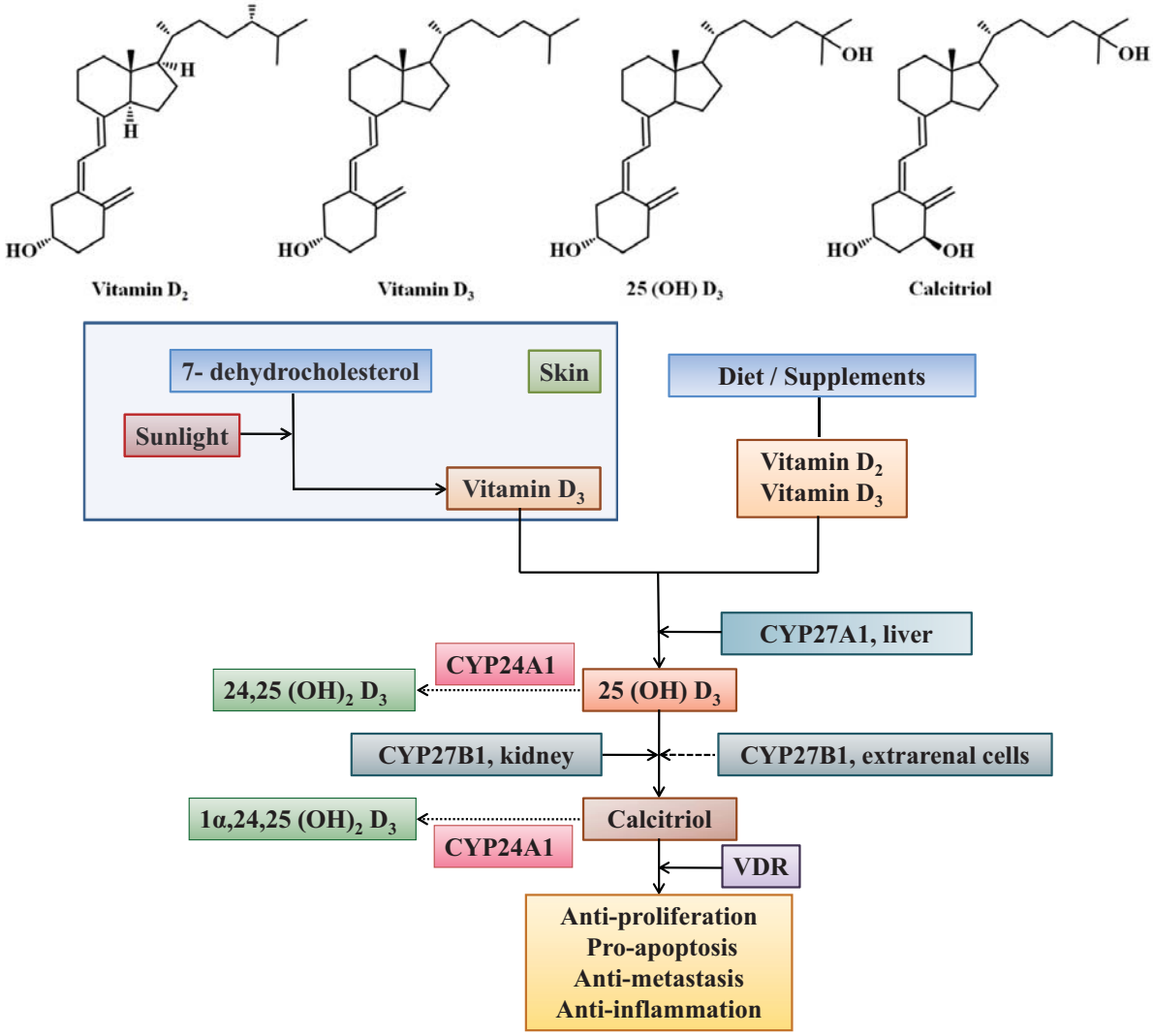

Fig. (1). The chemical structures and metabolism of vitamin D. The production of vitamin D in the skin resulted from sunlight exposure and the intake of vitamin D from diet or supplements are the main sources of vitamin D. It is then metabolized to calcitriol (active form of vitamin D_3) in the liver and kidney by the enzymes including 25-hydroxylase (CYP27A1) and 1α-hydroxylase (CYP27B1). Importantly, CYP27B1 also expresses in many other extrarenal tissues, including malignant cancer cells, to synthesize calcitriol and induce an autocrine/paracrine action of vitamin D_3.

regulates various transcriptional factors which play important roles in cancer progression [23,16]. Activation of vitamin D receptors can inhibit proliferation, angiogenesis and invasiveness in the intestinal tumors [24-26]. A comprehensive meta-analysis that performed on the association between the VDR polymorphisms and the risk of cancer (breast, skin and prostate) in Caucasian populations showed that a 6–7% reduction of cancer risk at any site was observed in those who carried at least one copy of the BsmI B allele; On the other hand, FokI ff genotype increased the cancer risk which was associated with vitamin D levels [22]. After binding to VDR, the primary molecular action of calcitriol is initiated. Consequently, a VDR-retinoid X receptor (RXR) heterodimer will be formed which interacts with specific DNA-binding sites (vitamin D response elements, VDREs) and finally induces the transcription of vitamin D responsive genes [27,25,28]. The degradation of calcitriol to 1, 24, $25(OH)_3D_3$ is initiated by 24-hydroxylase (CYP24A1) in response to 1, $25(OH)_2D$. $1,24,25(OH)_3$ D_3 will be in turn metabolized to excreted products such as calcitroic acid [13]. Such feedback mechanism helps to avoid vitamin D intoxication in our body.

RXR which consists of 3 subtypes (α, β and γ) is a family of nuclear receptors that regulate multiple signalling pathways [29]. The nuclear RXR is the preferential heterodimeric partner of VDR. Accumulative evidence has proven that the expression of RXR was positively associated with the risk of cancer [30-33]. Egan and colleagues indicated that allelic variation in RXRα, influences the risk of colorectal adenoma recurrence [30]. Jacobs *et al.* [31] also proved that RXRα single nucleotide polymorphisms (SNPs) rs7861779 and rs12004589 may be important markers for colorectal neoplasia. Studies also showed that decreased RXRβ expression may be related to the progression of prostate cancer [32]. Obara *et al.* [33] further demonstrated that the expression of RXRγ correlated with tumor stage, distant metastasis, and the 5-year cancer specific survival rate in patients with renal cell carcinoma. RXRs can be, therefore, identified as potential targets for cancer prevention and treatment.

THE EPIDEMIOLOGY OF VITAMIN D AND CANCER

Exposure to sunlight and/or intake of vitamin D from food are the major sources for human to get vitamin D. Epidemiological studies suggest that many factors that directly or indirectly influence the serum vitamin D levels, including vitamin D intake, sunlight exposure, geography and skin pigmentation and serum 25 (OH) D levels, are intimately correlated with cancer progression.

Vitamin D Intake

Dietary sources of vitamin D include 1) vitamin D_3 in some animal derived foods or animal products such as liver, egg yolk and fatty saltwater fish, 2) vitamin D_2 from plants, and 3) vitamin D fortified foods such as fortified milk and margarines [16]. It has been recommended that toxicity threshold is between 10,000 and 40,000 IU of vitamin D per day [34-36]. Several lines of evidence have shown that higher intakes of vitamin D from food and supplements and higher levels of vitamin D in the circulation are associated with lower cancer risk [37-42]. Individuals consume vitamin D supplements were observed to have a lower risk of adenoma recurrence [43]. A prostate, lung, colorectal, and ovarian cancer screening trial showed that dietary supplementation with more than 600 IU of vitamin D could reduce the risk of prostate cancer supporting the protective role of vitamin D [37]. In a recent randomized controlled trial, Lappe el al. [40] announced that postmenopausal women that provided with 1,100 IU/day of vitamin D_3 combined with 1400-1500 mg supplemental calcium/day, leaded to a 60% reduction of incidence of all invasive cancers. However, whether vitamin D can help reduce cancer risk or not is still debatable since controversial results were yielded in some epidemiologic studies in other cancers, such as breast cancer [44] and pancreatic cancer [45]. Noteworthy, failing to consider some important variables, such as the interaction of vitamin D with hormone treatment, other dietary supplements, seasonal change, and tobaccos, may lead to unreliable conclusions. For example, a reanalysis of data from the Women's Health Initiative (WHI) randomized trial has demonstrated a strong interaction between estrogen with the effects of calcium and vitamin D supplementation on colorectal cancer risk [46]. The calcium and vitamin D supplementation was beneficial only to the women assigned to placebo arms of the estrogen trials but not the women receiving estrogen therapy [46]. Therefore, well designed, large, randomized trials are in dire need to characterize the exact role of vitamin D in cancer.

Sunlight, Geography, and Skin Pigmentation

For most people, solar ultraviolet B (UVB) radiation is the major source of vitamin D [25]. UVB exposure has a significant protective effect in cancer incidence and mortality rate [47-48]. In addition, living at higher latitudes with lower sunlight exposure also associated with higher cancer mortality [49]. In a case-control study, men with more sunlight exposure or high occupational outdoor activities had obviously reduced risk of advanced prostate cancer [50]. Similarly, women who lived in the regions with high solar radiation in the National Health and Nutrition Examination Survey of the United States had about half the incidence of breast cancer than those lived in the regions with low solar radiation [51]. The survival of patients with colon cancer, breast cancer, prostate cancer and male patients with lung cancer in Norway were higher for those diagnosed in the summer and autumn rather than in the winter and spring due to the higher levers of Vitamin D production [52-53]. Increased incidences of pancreatic cancer and ovarian cancer were also observed among participants with low residential UVB exposure [54-55]. Moreover, the degree of skin pigmentation also influences vitamin D status. Negro subjects have been reported to require almost 10-50 times of exposure to UVB radiation to produce an equivalent amount of vitamin D than that does for Caucasian subjects [56,25].

Serum 25 (OH) D_3 Levels

As the major vitamin D metabolite in the circulation and the best indicator of overall vitamin D status, $25(OH)D_3$ is inversely associated with cancer incidence and recurrence [57-58]. Ren *et al.* [12] recently demonstrated that most gastric cancer patients were deficient in serum $25(OH)D_3$ and,

the clinical staging, e.g., lymph node invading or distant metastasis, were inversely correlated with patients' vitamin D levels. The association between prediagnosis plasma $25(OH)D_3$ levels and colorectal cancer mortality was also tested in the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS), which suggested that patients with higher plasma $25(OH)D_3$ levels were associated with a significant improvement in overall survival of colorectal cancer [59]. Moreover, a higher $25(OH)D_3$ level at surgery has been recently linked with a better survival rate of patients with colorectal cancer [60]. On the other hand, Freedman *et al.* [38] demonstrated in the Third National Health and Nutrition Examination Survey (NHANES III) cohort that there was a significant inverse relationship between colorectal cancer mortality and $25(OH)D_3$ levels. The mortality rate in the colorectal cancer Patients with serum $25(OH)D_3$ levels higher than 80 nmol/L had about three fourth less than those with $25(OH)D_3$ levels lower than 50 nmol/L. Further, Li and co-workers of the Physicians' Health Study cohort suggested that a large proportion of the US men had suboptimal vitamin D status and both $25(OH)D_3$ and $1,25(OH)_2D_3$ may play an important role in preventing prostate cancer progression [61].

VITAMIN D AND CANCER METASTASIS

In addition to the epidemiologic evidence, data from *in vitro* and *in vivo* studies also revealed that vitamin D has the anti-cancer effects. Flanagan *et al.* showed that $1,25(OH)_2D_3$ not only mediated breast cancer cell proliferation and apoptosis, but also inhibited cancer cell invasive ability [62]. Using the VDR transgenic mice, Nakagawa *et al.* [63] demonstrated that $VDR^{-/-}$ mice exhibited high serum levels of $1,25(OH)_2D_3$ which inhibited Lewis lung carcinoma cells metastasis. These results indicate that vitamin D may work as an intrinsic factor for the prevention of metastasis.

EMT has been considered as a critical step in cancer progression, especially in cancer metastasis in recent years [3-4]. EMT includes four important steps: 1) loss of epithelial cell adhesion, 2) expression of mesenchymal cell markers, 3) degradation of basement membranes, and 4) enhancement of cell migration and invasion that facilitate tumor cells' invasion into stroma and entrance to the circulation. A typical symbol of EMT is the loss of the expression of cell-cell adhesion molecule E-cadherin and the gain of mesenchymal markers (vimentin, fibronectin, N-cadherin and others) [64]. *In vitro* and *in vivo* studies have suggested that vitamin D could effectively inhibit EMT. Calcitriol, the biologically active form of vitamin D, has been demonstrated to inhibit β-catenin transcriptional activity which has been shown to be important for Wnt signal induced EMT [65-66] by promoting VDR binding to β-catenin, which in turn results in the induction of the expression of E-cadherin in colon cancer cells [67]. Calcitriol can also inhibit the Wnt/β-catenin signaling pathway by increasing the expression of two genes that encode the extracellular Wnt inhibitors DICKKOPF-1 and DICKKOPF-4 (DKK-1, DKK-4) [67]. Adhesion of circulating cancer cells to the microvascular endothelium is one of the key steps for cancer metastasis. Hsu *et al.* [8] found that calcitriol was able to increase the expression of E-cadherin in prostate cancer cells and promote the homotypic cell-cell aggregation that further prevent the circulating cancer cells to adhere to microvascular endothelial cells and finally reduce the metastatic potential. Calcitriol and its analogues EB1089 and KH1060 can suppress the expression of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) and results in potentially beneficial effects on metabolic disorders [68]. The modulation of the expression of α6 and β4 integrins is also an important mechanism for calcitriol to enhance cancer cell adhesion [69]. A recent study showed that E-cadherin was down-regulated by the activation of epidermal growth factor (EGF) receptor (EGFR) via the up-regulation of Snail, whereas, calcitriol could decrease the expression of EGFR, indicating that calcitriol may promote E-cadherin expression through the inhibition of EGFR/Snail signaling [70-71].

Cystatin D could inhibit the migration of human colon cancer cells via repressing the expression of the EMT inducers, such as Snail, Slug, ZEB1 and ZEB2, and conversely, inducing the expression of E-cadherin and other adhesion proteins [72]. Based on a transcriptomic analysis performed in human colon cancer cells, calcitriol is able to increase the level of cystatin D [73]. Alvarez-Diaz *et al.* [72] demonstrated that calcitriol could induce VDR to activate the cystatin D promoter and increase cystatin D expression. The transcriptomic analysis also revealed a decrease in the level of Sprouty-2 (SPRY2), a negative feedback regulator of several receptor tyrosine kinase receptors including EGFR, RNA on the treatment with calcitriol [73]. Barbachano and colleagues recently found that SPRY2 gene and its induced EMT related gene ZEB1 were inhibited by calcitriol in colon cancer cells which in part due to the induction of E-cadherin mediated cell adhesion [74]. As a histone H3 lysine demethylase, JmjC domain-containing protein 3 (JMJD3) is up-regulated by $1,25(OH)_2D_3$ in colon cancer cells [75], which imply that vitamin D might influence EMT process via JMJD3. In addition, calcitriol can also decrease the expression of mesenchymal markers, such as N-cadherin, α-smooth muscle actin (α-SMA) and fibronection in tumor cells, which further supports the idea that vitamin D can inhibit the EMT [76-77]. Increasing evidence has shown that Snail and some other EMT related transcriptional factors can repress VDR expression with a loss of responsiveness to calcitriol, thus suppressed VDR expression may be regarded as an indicator for patients who are not able to respond to vitamin D related therapy [78-81].

Matrix metalloproteinases (MMPs), plasminogen activator (PAs) and cathepsins (CPs) are the enzymes that mediate the degradation of the extracellular matrix and the basement membrane of the vascular epithelium and consequently allow the cancer cells to invade through the matrix and capillaries for further metastasis [9,82,15]. These three proteases are negatively regulated by tissue inhibitors of metalloproteinases (TIMPs), plasminogen activator inhibitors (PAIs) and cathepsin inhibitors (CIs), respectively [15]. Decreased expression levels of urokinase PA, tissue-type PA, MMP-2 and MMP-9 in cancer patients often linked with tumor metastasis [83]; in response to calcitriol and its analogues, the expression levels of these enzymes were decreased while the expression of plasminogen activator inhibitors (PAIs) was increased in breast, lung and prostate cancer cells [84-87]. In prostate cancer cells, calcitriol could not only decrease the expression of MMP-9 and CPs but also increase the activity

of their counterparts, tissue inhibitor of metalloproteinases (TIMP)-1 and cathepsin inhibitors (CIs) [84]. Moreover, Tenascin-C, an extracellular matrix protein with the ability to promote tumor growth, invasion and angiogenesis, can be inhibited by calcitriol in a variety of normal or malignant mouse and human epithelial cell lines [88]. As a product of selective deglycosylation of DBP, vitamin D binding protein-macrophage activating factor (DBP-maf) has been proved to be an anti-tumorigenic agent [89]. Gregory *et al.* [90] recently showed that DBP-maf was able to cause the reduction in expressing urokinase PA receptor (uPAR) and in turn inhibited the migratory and invasive ability of prostate cancer cells. DBP-maf can also enhance the cell-cell adhesion through the reduction of vimentin expression, which indicating a reversal effect of EMT [91] **(**Fig. **2)**.

CD44 is a multifunctional transmembrane glycoprotein involved in cell adhesion, invasion, angiogenesis and metastasis, and recognized as a key marker of cancer stem cells in many cancers, such as prostate, breast and pancreatic cancer [92-94]. A recent study showed that calcitriol inhibited the expression of CD44 and enhanced the expression of E-cadherin in colon cancer, which may lead to the inhibitory effect on $Apc^{Min/+}$- driven tumorigenesis [95]. CD44 has multiple variants produced by alternative splicing [96], among which CD44v (100-250 kDa) rather than CD44s (85 kDa) has been strongly associated with cancer metastasis[97]. CD44v3 and CD44v6, which are related to cancer cell invasion, migration and metastasis, have been proved to be inhibited by a novel Gemini vitamin D analog, BXL0124 in breast cancer [98,94]. So *et al.* found that BXL0124 given intraperitoneally at the dose of 0.1 g/kg body weight suppressed 75% tumor size and 66% tumor weight in SCID mice. BXL0124 also inhibits the expression levels of CD44 protein and mRNA in highly aggressive breast cancer cell line MCF10DCIS in a dose dependent manner [94]. A further study from the same group found that the expression level of VDR protein was increased while the expression level of CD44 protein was suppressed by BXL0124 treatment in MCF10CA1a and MDA-MB-468 cells [99]. Using cDNA microarrays, Krishnan *et al.* [100] identified many vitamin D-regulated genes, of which the N-myc downstream regulated 1(NDRG1), also known as Drg 1, being suppressed in prostate cancer [101] was up-regulated by vitamin D. NDRG1 has also been demonstrated to inhibit colorectal metastasis by inducing differentiation and reversing the metastatic phenotype [102]. Therefore, the up-regulation of NDRG1 is likely a mechanism for the anti-metastatic action of vitamin D. Interleukin-6 (IL-6), which is a p38-regulated pleiotropic cytokine, was elevated and positively correlated with tumor burden and the number of bone metastases in prostate cancer [103]. Nonn *et al.* [104] demonstrated that vitamin D could reduce IL-6 production through the inhibition of p38 via MKP5. Furthermore, transcription factor Stat3 is involved in metastatic behavior of human prostate cancer cells [105]. Over-expression of Stat3 induced the formation of lamellipodia and promoted a migratory phenotype of cancer cells [105]. Recent studies have shown that vitamin D might interfere with Stat3 activation and therefore intake of vitamin D may provide therapeutic value to the cancer patients by reducing Stat3 [106].

Bone is one of the most preferential metastatic target sites for cancer cells [107]. Bone resorption is important for cancer cell metastasis. Cancer cells can produce the bone-resorbing cytokines and increase osteoclastic bone resorption, which in turn promote cancer cells to get abundant supplies of bone-stored growth factors [108]. This vicious cycle promotes both bone resorption and cancer cell growth. Using a bone metastasis model established by Arguello *et al.* [109],

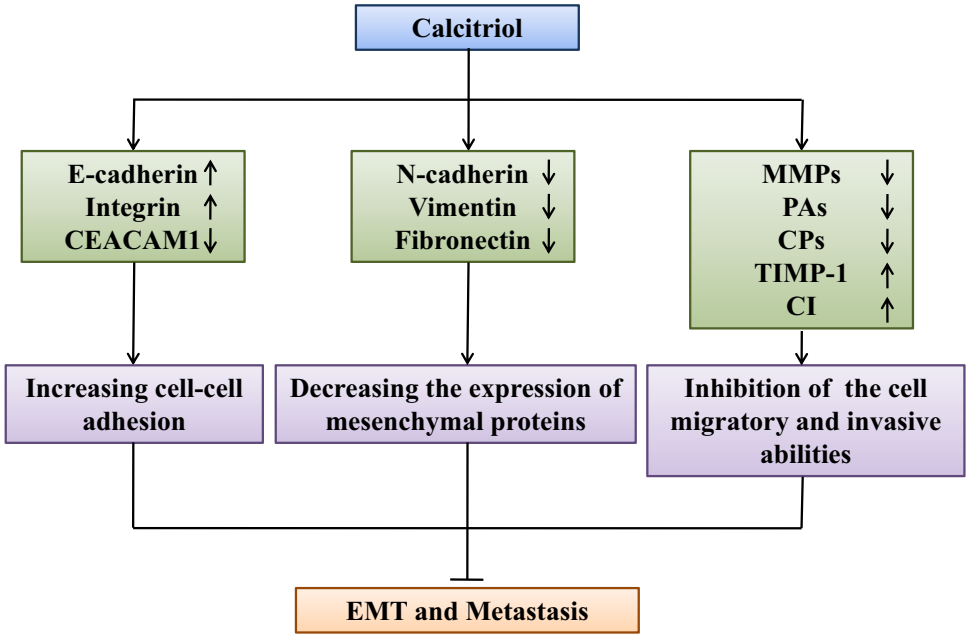

Fig. (2). The molecular mechanisms of the anti-EMT actions of calcitriol. Calcitriol can inhibit the process of EMT by 1) increasing epithelial cell adhesion [8, 65-74], 2) decreasing the expression of mesenchymal protein markers [76-81], 3) inhibiting the expression of proteases that in turn halt the degradation of basement membranes and negatively modulate the cancer cell migratory and invasive abilities [9, 15, 82-91].

El Abdaimi and colleagues found that vitamin D analogue EB 1089 could reduce not only the development of osteolytic bone metastases but also the tumor burden within bone [110]. Evidence has shown that vitamin D deficiency could increase both the growth of tumors and the osteoclastic activity in the tibiae of mice following intra-tibial implantation of breast cancer cells [111]. Evidence also showed that intratibially implanted prostate cancer cells resulted in mixed osteolytic and osteosclerotic lesion. Vitamin D deficiency stimulates prostate cancer growth in bone via the modulation of bone microenvironment [112].

Bhatia *et al.* [113] showed that the noncalcemic vitamin D analogue EB1089 (seocalcitol, 1α-dihydroxy-22,24-diene-24,26,27-trihomovitaminD3) could inhibit the parathyroid hormone-related protein (PTHrP)-enhanced bone metastasis and xenograft growth as well as intra-tumor vessel density of human prostate cancer. Paricalcitol, another synthetic analog of vitamin D (19-nor-1α-25-dihydroxyvitamin D2), has been approved by the Food and Drug Administration for the clinical treatment of secondary hyperparathyroidism. Park *et al.* [10] recently proved that treatment with paricalcitol not only inhibited gastric cancer cell growth and induced cell cycle arrest, but also induced apoptosis and showed anti-inflammatory activity. Moreover, the growth of intraperitoneal metastases *in vivo* was reduced in mice treated with paricalcitol. Besides, a novel Gemini vitamin D analog, BXL0124 [1α,25-dihydroxy-20R-21 (3-hydroxy -3-deuteromethy l-4,4,4-trideuterobutyl)-23-yne-26,27-hexafluro-cholecalciferol) was able to repress the expression of CD44, which further resulted in a decreased amount of the CD44-STAT3-JAK2 complex and inhibited the invasive ability of the basal-like breast cancer [99].

VITAMIN D AND CANCER ANGIOGENESIS

Angiogenesis, the formation of new blood vessels from existing vasculatures, is connected with cancer invasion and metastasis tightly [114]. In tumor-derived endothelial cells (TDECs), calcitriol inhibits the proliferation via promoting G0-G1 cell cycle arrest and induces apoptosis [115-116]. These effects observed in TDECs are accompanied by the modulation of cell cycle proteins (induction of p27 and down-regulation of p21 protein expression), anti-apoptotic protein (down-regulation of bcl-2), survival markers (down-regulation of phosphorylated-Akt and phosphorylated-Erk) and the cleavage of caspase-3 [115-116]. Interestingly, the anti-proliferating and pro-apoptotic effects of calcitriol do not occur in normal endothelial cells (mouse embryonic yolk sac endothelial cells or Matrigel-derived endothelial cells) [117,116]. This phenomenon may due to the higher binding affinity of VDR for calcitriol in TDEC than that in normal endothelial cells [116]. Chung *et al.* [117] proved that the sensitivity of TDECs to calcitriol is attributed to epigenetic silencing of CYP24. Recently, by comparing the effects of calcitriol on transgenic adenocarcinoma of the mouse prostate (TRAMP)-2 tumors in either VDR wild type (WT) or knockout (KO) mice, Chung and colleagues further demonstrated that calcitriol mediated growth inhibition on TDECs is VDR-dependent [23].

Hypoxia, a common pathophysiologic condition in many cancers promotes cancer progression via stimulating many cellular events including angiogenesis. Cells are 100–150 mm away from blood vessels experiencing diffusion-limited chronic hypoxia, which is very common in the fast growing tumors due to the intermittent blood supply caused by abnormal tumor vasculature [118]. Stimulation of angiogenesis in response to hypoxia is mediated by hypoxia-induced factor-1(HIF-1), which is a heterodimeric transcription factor that consists of HIF-1α and β subunits. Under normoxic conditions, HIF-1α is rapidly degraded, whereas under hypoxic condition, HIF-1α is stabilized and heterodimerizes with HIF-1β and lead to the up-regulation of many hypoxia-response proteins, including endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), VEGF receptor-1 (Flt-1) and glucose transporter-1 (Glut-1) [119-120]. VEGF, the most potent stimulator of angiogenesis, binds to its receptor on the vascular endothelial cells of nearby blood vessels and promotes cell proliferation, migration and invasion into the tumor [121]. It has been shown that calcitriol possesses anti-angiogenic activities by suppressing VEGF signaling *in vitro* and *in vivo* [122-123,86]. VEGF-induced endothelial cell tube formation and tumor vascularization could be inhibited by calcitriol in mice bearing xenografts of VEGF-over-expressing breast cancer cells [123]. Ben-Shoshan *et al.* [122] demonstrated that calcitriol can not only reduce the protein expression of HIF-1α and VEGF in various human cancer cells, but also inhibit HIF-1 transcriptional activity as well as HIF-1 target genes, such as VEGF, ET-1 and Glut-1. Calcitriol reduced VEGF expression might be attributed to the transcriptional repression of HIF-1 [122]. In addition to VEGF, the angiopoietins, Ang-1 and Ang-2, can also enhance the maturation and stabilization of newly formed blood vessels via the tyrosine kinase receptor Tie-2 [124]. Although evidence has shown that Ang1 does not stimulate proliferation of endothelial cells, it can induce endothelial survival, sprouting, migration and tube formation [125]. On the other hand, Ang2 destabilizes the vasculature and in turn makes the endothelial cells more sensitive to the angiogenic signals [126]. Studies have also shown the inhibition effect of calcitriol on both Ang-1 and Ang-2 [127-128]. Moreover, calcitriol can also modulate the expression of the potent anti-angiogenic factor thrombospondin-1in human colon carcinoma cells [129].

As the controller of DNA transcription, nuclear factor κB (NF-κB) not only regulates the immune responses and inflammation, but also contributes to the malignant behavior, including metastasis and angiogenesis, by increasing the transcription of proteolytic enzymes such as MMP9, uPA and uPA receptor or angiogenic factors such as Interleukin -8 (IL-8) and VEGF [130]. IL-8, a multifunctional inflammatory cytokine, has been proved to regulate pathological angiogenesis [131]. Calcitriol is known to modulate the NF-κB activity in many cancer cells, including breast cancer and prostate cancer [132-133]. Calcitriol can also inhibit the expression of the proangiogenic factor IL-8 in an NF-κB dependent manner [134]. Hepatocyte growth factor (HGF) is a mitogen for epithelial cells that stimulates vascular endothelial cell migration, proliferation, and organization into capillary-like tubes, and also promotes tumor invasiveness and angiogenesis [135]. It has been demonstrated that calcitriol can suppress the synthesis and secretion of HGF [136]. Calcitriol hence may inhibit tumor angiogenesis via suppression

of HGF. In addition, calcitriol can also inhibit NF-κB by indirectly up-regulating the expression of insulin-like growth factor binding protein-3 (IGFBP-3), which has been reported to suppress tumor growth and angiogenesis by both Insulin-like growth factor (IGF)-dependent and IGF-independent mechanisms [137-138].

Cycloxygenase-2 (COX-2), the enzyme responsible for prostaglandins (PGs) synthesis, is associated with tumor growth, angiogenesis, lymphatic invasion, and metastasis [139-141]. Most actions of COX-2 are known to be mediated by prostaglandin E2 (PGE2). Chang *et al.* [142] demonstrated that PGE2 could stimulate the expression of angiogenic regulatory genes in mammary tumor cells isolated from COX-2 transgenic mice, which indicated that COX-2-derived PGE2, a potent inducer of angiogenic switch during mammary cancer progression may play its important role by increasing the expression of HIF-1α protein [143]. Excess PGE2 that undergoes metabolic inactivation is catalyzed by 15-hydroxyprostaglandin dehydrogenase (15-PGDH) [144]. 15-PGDH has been shown to act as a tumor suppressor in a variety of cancers [145-148]. Calcitriol regulates the expression of several genes under PG pathway in human cancer cells [149-150]. Swami *et al.* [150] showed that calcitriol could inhibit the PG pathway in 3 separate ways: by decreasing COX-2 expression, stimulating 15-PGDH expression, and decreasing PG receptors EP2 and FP. The suppression of PG pathway can therefore be deemed as an important additional mechanism for calcitriol-induced anti-angiogenesis.

Moreover, as mentioned above, MMPs also play an important role in cancer angiogenesis, because MMP-induced degradation of extracellular matrix and disruption of capillary basement membrane are vital for endothelial cell migration and invasion [126]. Vitamin D induced proteases suppression is an essential mechanism for anti-angiogenic treatment **(**Fig. **3)**.

CONCLUSIONS AND FUTURE PERSPECTIVES

Many epidemiologic studies suggest that vitamin D and the vitamin D metabolic contributors such as sunlight, geography and vitamin D-metabolizing enzymes are related with cancer progression and outcomes. Clinical trials showed that $1,25(OH)_2D_3$ in combination with other anticancer agents demonstrate synergistic interactions [151-154]. Recently, several clinical trials reported to use $1,25(OH)_2D_3$ plus paclitaxel and $1,25(OH)_2D_3$ plus gefitinib [155-156] for the treatment of advanced malignancies, and $1,25(OH)_2D_3$ plus carboplatin and $1,25(OH)_2D_3$ plus docetaxel for the treatment of prostate cancer [157-158]. However, most of these studies are only based on persuasive preclinical data, and thus, the use of 1, $25(OH)_2D_3$ as a single agent is limited due

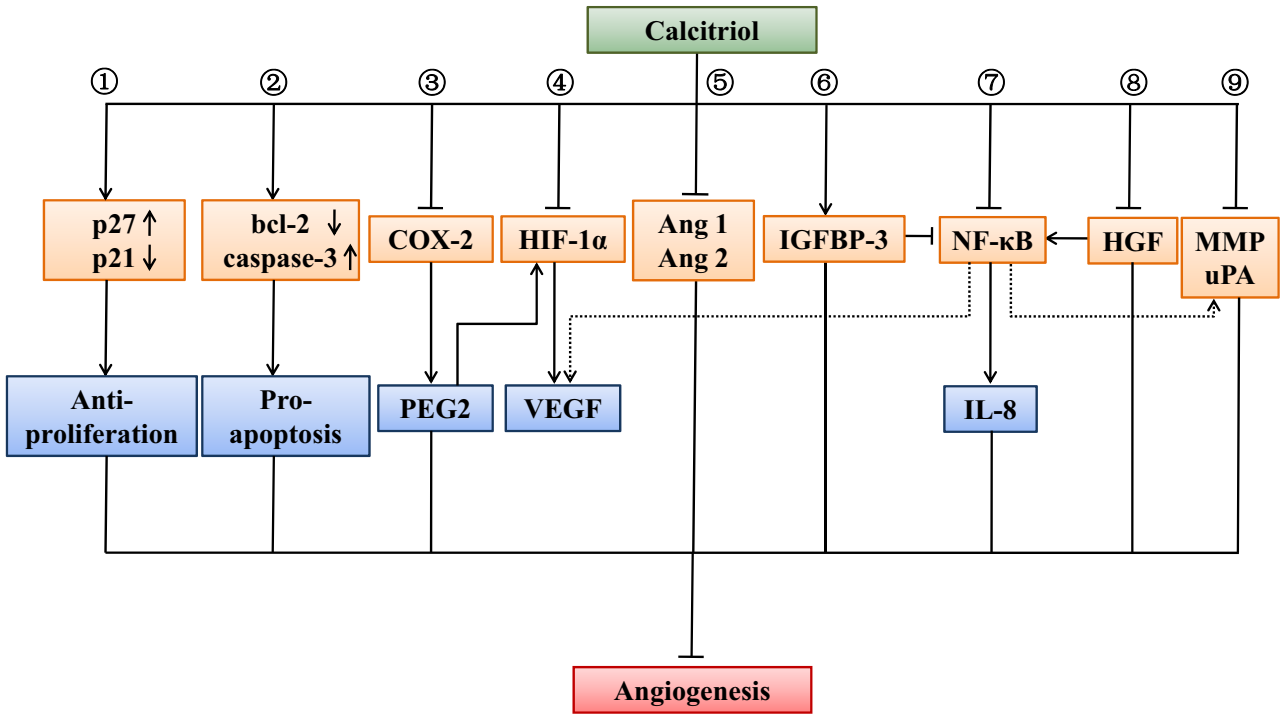

Fig. (3). The molecular pathways that participate in the anti-angiogenesis action of calcitriol. Calcitriol can suppress tumor angiogenesis by the following mechanisms: 1) modulation of tumor-derived endothelial cells (TDECs) cycle proteins (p27 and p21) [115-117]; 2) induction of the apoptosis of TDECs [115-117]; 3) inhibition of Cycloxygenase-2 (COX-2) and prostaglandin E2 (PGE2) expression that can further increase hypoxia-induced factor-1α (HIF-1α) expression [149-150]; 4) suppression of the expression of pro-angiogenic factors including HIF-1α and vascular endothelial growth factor (VEGF) [86, 122-123]; 5) inhibition of the Ang-1 and Ang-2 expressions [127-128]; 6) up-regulation of the expression of insulin-like growth factor binding protein-3 (IGFBP-3), which suppresses tumor angiogenesis and nuclear factor κB (NF-κB) activation [137-138]; 7) inhibition of NF-κB signaling that further modulating the expression of VEGF, Interleukin -8 (IL-8) and proteases [132-134]; 8) down-regulation of hepatocyte growth factor (HGF) that can promote tumor angiogenesis and NF-κB activation[135-136] and 9) decreasing the expression of matrix metalloproteinases (MMPs) and urokinase plasminogen activator (uPA) [9, 15, 82-84, 126].

to lack of dose, toxicity and pharmacokinetic data, which not usually confronted in phase I studies in cancer. Here, we summarized the effects and possible mechanisms of vitamin D with a focus on its anti-metastatic and anti-angiogenic activities. Compelling evidence suggests vitamin D's anti-metastatic effects may attribute to its influence on the progression of EMT. Calcitriol can not only increase the expression of epithelial proteins and decrease mesenchymal proteins' expression but also inhibit the expression of proteases that in turn halted the degradation of basement membranes and negatively modulated the cancer cell migratory and invasive ability. The anti-angiogenesis effects of vitamin D have been implicated with its inhibition of TDECs growth and suppression of the expression of many pro-angiogenic factors, including HIF-1, VEGF and Ang1. Additionally, anti-inflammatory effects including inhibition of PG synthesis and NF-κB activation may also contribute to the anti-angiogenesis effects of vitamin D. Therefore, vitamin D, calcitriol or its analogs may represent promising therapeutic strategies targeting cancer metastasis and angiogenesis. Well-designed experimental and clinical studies with dietary vitamin D or calcitriol/analogs therapies as well as combination therapies with other drugs are anticipated for uncovering the therapeutic opportunity of using vitamin D for the improvement of cancer prevention and treatment.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

α-SMA	=	α-smooth muscle actin
Ang1	=	Angiopoeitin 1
CEACAM1	=	Carcinoembryonic antigen-related cell adhesion molecule 1
CIs	=	Cathepsin inhibitors
COX-2	=	Cycloxygenase-2
CPs	=	Cathepsins
DBP	=	Vitamin D binding protein
EGF	=	Epidermal growth factor
EMT	=	Epithelial-mesenchymal transition
ET-1	=	Endothelin-1
Glut-1	=	Glucose transporter-1
HGF	=	Hepatocyte growth factor
HIF-1α	=	Hypoxia-induced factor-1α
IGFBP-3	=	Insulin-like growth factor binding protein-3
IL-6	=	Interleukin-6
MAPK	=	Mitogen-activated protein kinase
MKP5	=	Mitogen-activated protein kinase phosphatase 5
MMPs	=	Matrix metalloproteinases
PAs	=	Plasminogen activator
PDGF	=	Platelet-derived growth factor
PGE2	=	Prostaglandin E2
TDECs	=	Tumor-derived endothelial cells
TIMPs	=	Tissue inhibitors of metalloproteinases
VDR	=	Vitamin D receptor
VEGF	=	Vascular endothelial growth factor

REFERENCES

[1] Siegel, R.; Naishadham, D.; Jemal, A. Cancer statistics, 2012. *CA. Cancer J. Clin.*, **2012**, *62*(1), 10-29.

[2] Gupta, G. P.; Massague, J. Cancer metastasis: building a framework. *Cell*, **2006**, *127*(4), 679-695.

[3] Iwatsuki, M.; Mimori, K.; Yokobori, T.; Ishi, H.; Beppu, T.; Nakamori, S.; Baba, H.; Mori, M. Epithelial-mesenchymal transition in cancer development and its clinical significance. *Cancer Sci.*, **2010**, *101*(2), 293-299.

[4] Satelli, A.; Li, S. Vimentin in cancer and its potential as a molecular target for cancer therapy. *Cell Mol. Life Sci.*, **2011**, *6* (18), 3033-3046.

[5] Folkman, J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat. Med.*, **1995**, *1*(1), 27-31.

[6] Khan, N.; Afaq, F.; Mukhtar, H. Apoptosis by dietary factors: the suicide solution for delaying cancer growth. *Carcinogenesis*, **2007**, *28*(2), 233-239.

[7] Surh, Y. J. Cancer chemoprevention with dietary phytochemicals. *Nat. Rev. Cancer*, **2003**, *3*(10), 768-780.

[8] Hsu, J. W.; Yasmin-Karim, S.; King, M. R.; Wojciechowski, J. C.; Mickelsen, D.; Blair, M. L.; Ting, H. J.; Ma, W. L.; Lee, Y. F. Suppression of prostate cancer cell rolling and adhesion to endothelium by 1alpha,25-dihydroxyvitamin D3. *Am. J. Pathol.*, **2011**, *178*(2), 872-880.

[9] Krishnan, A. V.; Feldman, D. Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. *Annu. Rev. Pharmacol. Toxicol.*, **2011**, *51,* 311-336.

[10] Park, M. R.; Lee, J. H.; Park, M. S.; Hwang, J. E.; Shim, H. J.; Cho, S. H.; Chung, I. J.; Bae, W. K. Suppressive effect of 19-nor-1alpha-25-dihydroxyvitamin D2 on gastric cancer cells and peritoneal metastasis model. *J. Korean Med. Sci.*, **2012**, *27*(9), 1037-1043.

[11] Goodwin, P. J.; Ennis, M.; Pritchard, K. I.; Koo, J.; Hood, N. Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. *J. Clin. Oncol.*, **2009**, *27*(23), 3757-3763.

[12] Ren, C.; Qiu, M. Z.; Wang, D. S.; Luo, H. Y.; Zhang, D. S.; Wang, Z. Q.; Wang, F. H.; Li, Y. H.; Zhou, Z. W.; Xu, R. H. Prognostic effects of 25-hydroxyvitamin D levels in gastric cancer. *J. Transl. Med.*, **2012**, *10*(1), 16.

[13] Trump, D. L.; Deeb, K. K.; Johnson, C. S. Vitamin D: considerations in the continued development as an agent for cancer prevention and therapy. *Cancer J.*, **2010**, *16*(1), 1-9.

[14] Cross, H. S. Extrarenal vitamin D hydroxylase expression and activity in normal and malignant cells: modification of expression by epigenetic mechanisms and dietary substances. *Nutr. Rev.*, **2007**, *65* (8 Pt 2), S108-112.

[15] Vanoirbeek, E.; Krishnan, A.; Eelen, G.; Verlinden, L.; Bouillon, R.; Feldman, D.; Verstuyf, A. The anti-cancer and anti-inflammatory actions of 1,25(OH)D. *Best Pract. Res. Clin. Endocrinol. Metab.*, **2011**, *25*(4), 593-604.

[16] Deeb, K. K.; Trump, D. L.; Johnson, C. S. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nat. Rev. Cancer*, **2007**, *7*(9), 684-700.

[17] Lopes, N.; Sousa, B.; Martins, D.; Gomes, M.; Vieira, D.; Veronese, L. A.; Milanezi, F.; Paredes, J.; Costa, J. L.; Schmitt, F.

Alterations in Vitamin D signalling and metabolic pathways in breast cancer progression: a study of VDR, CYP27B1 and CYP24A1 expression in benign and malignant breast lesions. *BMC Cancer*, **2010**, *10,* 483.

[18] McCarthy, K.; Laban, C.; Bustin, S. A.; Ogunkolade, W.; Khalaf, S.; Carpenter, R.; Jenkins, P. J. Expression of 25-hydroxyvitamin D-1-alpha-hydroxylase, and vitamin D receptor mRNA in normal and malignant breast tissue. *Anticancer Res.*, **2009**, *29*(1), 155-157.

[19] Bises, G.; Kallay, E.; Weiland, T.; Wrba, F.; Wenzl, E.; Bonner, E.; Kriwanek, S.; Obrist, P.; Cross, H. S. 25-hydroxyvitamin D3-1alpha-hydroxylase expression in normal and malignant human colon. *J. Histochem. Cytochem.*, **2004**, *52*(7), 985-989.

[20] Cooke, N. E.; David, E. V. Serum vitamin D-binding protein is a third member of the albumin and alpha fetoprotein gene family. *J. Clin. Invest.*, **1985**, *76*(6), 2420-2424.

[21] Fleet, J. C.; DeSmet, M.; Johnson, R.; Li, Y. Vitamin D and cancer: a review of molecular mechanisms. *Biochem. J.*, **2012**, *441*(1), 61-76.

[22] Raimondi, S.; Johansson, H.; Maisonneuve, P.; Gandini, S. Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. *Carcinogenesis*, **2009**, *30*(7), 1170-1180.

[23] Chung, I.; Han, G.; Seshadri, M.; Gillard, B. M.; Yu, W. D.; Foster, B. A.; Trump, D. L.; Johnson, C. S. Role of vitamin D receptor in the antiproliferative effects of calcitriol in tumor-derived endothelial cells and tumor angiogenesis *in vivo*. *Cancer Res.*, **2009**, *69*(3), 967-975.

[24] Evans, S. R.; Shchepotin, E. I.; Young, H.; Rochon, J.; Uskokovic, M.; Shchepotin, I. B. 1,25-dihydroxyvitamin D3 synthetic analogs inhibit spontaneous metastases in a 1,2-dimethylhydrazine-induced colon carcinogenesis model. *Int. J. Oncol.*, **2000**, *16*(6), 1249-1254.

[25] Giovannucci, E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control*, **2005**, *16*(2), 83-95.

[26] Hubner, R. A.; Muir, K. R.; Liu, J. F.; Logan, R. F.; Grainge, M. J.; Houlston, R. S. Dairy products, polymorphisms in the vitamin D receptor gene and colorectal adenoma recurrence. *Int. J. Cancer*, **2008**, *123*(3), 586-593.

[27] Byers, S. W.; Rowlands, T.; Beildeck, M.; Bong, Y. S. Mechanism of action of vitamin D and the vitamin D receptor in colorectal cancer prevention and treatment. *Rev. Endocr. Metab. Disord.*, **2011**, *13*(1), 31-38.

[28] Thorne, J.; Campbell, M. J. The vitamin D receptor in cancer. *Proc. Nutr. Soc.*, **2008**, *67*(2), 115-127.

[29] Ahuja, H. S.; Szanto, A.; Nagy, L.; Davies, P. J. The retinoid X receptor and its ligands: versatile regulators of metabolic function, cell differentiation and cell death. *J. Biol. Regul. Homeost. Agents*, **2003**, *17*(1), 29-45.

[30] Egan, J. B.; Thompson, P. A.; Ashbeck, E. L.; Conti, D. V.; Duggan, D.; Hibler, E.; Jurutka, P. W.; Leroy, E. C.; Martinez, M. E.; Mount, D.; Jacobs, E. T. Genetic polymorphisms in vitamin D receptor VDR/RXRA influence the likelihood of colon adenoma recurrence. *Cancer Res.*, **2010**, *70*(4), 1496-1504.

[31] Jacobs, E. T.; Martinez, M. E.; Campbell, P. T.; Conti, D. V.; Duggan, D.; Figueiredo, J. C.; Haile, R. W.; LeRoy, E. C.; Poynter, J. N.; Thompson, P. A.; Baron, J. A. Genetic variation in the retinoid X receptor and calcium-sensing receptor and risk of colorectal cancer in the Colon Cancer Family Registry. *Carcinogenesis*, **2010**, *31*(8), 1412-1416.

[32] Lotan, Y.; Xu, X. C.; Shalev, M.; Lotan, R.; Williams, R.; Wheeler, T. M.; Thompson, T. C.; Kadmon, D. Differential expression of nuclear retinoid receptors in normal and malignant prostates. *J. Clin. Oncol.*, **2000**, *18*(1), 116-121.

[33] Obara, W.; Konda, R.; Akasaka, S.; Nakamura, S.; Sugawara, A.; Fujioka, T. Prognostic significance of vitamin D receptor and retinoid X receptor expression in renal cell carcinoma. *J. Urol.*, **2007**, *178*(4 Pt 1), 1497-1503.

[34] Miller, P. D. Vitamin D, calcium, and cardiovascular mortality: a perspective from a plenary lecture given at the annual meeting of the American Association of Clinical Endocrinologists. *Endocr. Pract.*, **2011**, *17*(5), 798-806.

[35] Rizzoli, R.; Boonen, S.; Brandi, M. L.; Bruyere, O.; Cooper, C.; Kanis, J. A.; Kaufman, J. M.; Ringe, J. D.; Weryha, G.; Reginster, J. Y. Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Curr. Med. Res. Opin.*, **2013**, *29*(4), 305-313.

[36] Ross, A. C.; Manson, J. E.; Abrams, S. A.; Aloia, J. F.; Brannon, P. M.; Clinton, S. K.; Durazo-Arvizu, R. A.; Gallagher, J. C.; Gallo, R. L.; Jones, G.; Kovacs, C. S.; Mayne, S. T.; Rosen, C. J.; Shapses, S. A. The 2011 Dietary Reference Intakes for Calcium and Vitamin D: what dietetics practitioners need to know. *J. Am. Diet. Assoc.*, **2011**, *111*(4), 524-527.

[37] Ahn, J.; Albanes, D.; Peters, U.; Schatzkin, A.; Lim, U.; Freedman, M.; Chatterjee, N.; Andriole, G. L.; Leitzmann, M. F.; Hayes, R. B. Dairy products, calcium intake, and risk of prostate cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol. Biomarkers Prev.*, **2007**, *16*(12), 2623-2630.

[38] Freedman, D. M.; Looker, A. C.; Chang, S. C.; Graubard, B. I. Prospective study of serum vitamin D and cancer mortality in the United States. *J. Natl. Cancer Inst.*, **2007**, *99*(21), 1594-1602.

[39] Garland, C. F.; Garland, F. C.; Gorham, E. D.; Lipkin, M.; Newmark, H.; Mohr, S. B.; Holick, M. F. The role of vitamin D in cancer prevention. *Am. J. Public Health*, **2006**, *96*(2), 252-261.

[40] Lappe, J. M.; Travers-Gustafson, D.; Davies, K. M.; Recker, R. R.; Heaney, R. P. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am. J. Clin. Nutr.*, **2007**, *85*(6), 1586-1591.

[41] Lieberman, D. A.; Prindiville, S.; Weiss, D. G.; Willett, W. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA*, **2003**, *290*(22), 2959-2967.

[42] Wei, M. Y.; Garland, C. F.; Gorham, E. D.; Mohr, S. B.; Giovannucci, E. Vitamin D and prevention of colorectal adenoma: a meta-analysis. *Cancer Epidemiol. Biomarkers Prev.*, **2008**, *17*(11), 2958-2969.

[43] Hartman, T. J.; Albert, P. S.; Snyder, K.; Slattery, M. L.; Caan, B.; Paskett, E.; Iber, F.; Kikendall, J. W.; Marshall, J.; Shike, M.; Weissfeld, J.; Brewer, B.; Schatzkin, A.; Lanza, E. The association of calcium and vitamin D with risk of colorectal adenomas. *J. Nutr.*, **2005**, *135*(2), 252-259.

[44] Chlebowski, R. T.; Johnson, K. C.; Kooperberg, C.; Pettinger, M.; Wactawski-Wende, J.; Rohan, T.; Rossouw, J.; Lane, D.; O'Sullivan, M. J.; Yasmeen, S.; Hiatt, R. A.; Shikany, J. M.; Vitolins, M.; Khandekar, J.; Hubbell, F. A. Calcium plus vitamin D supplementation and the risk of breast cancer. *J. Natl. Cancer Inst.*, **2008**, *100*(22), 1581-1591.

[45] Stolzenberg-Solomon, R. Z.; Vieth, R.; Azad, A.; Pietinen, P.; Taylor, P. R.; Virtamo, J.; Albanes, D. A prospective nested case-control study of vitamin D status and pancreatic cancer risk in male smokers. *Cancer Res.*, **2006**, *66*(20), 10213-10219.

[46] Ding, E. L.; Mehta, S.; Fawzi, W. W.; Giovannucci, E. L. Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women's Health Initiative randomized trial. *Int. J. Cancer*, **2008**, *122*(8), 1690-1694.

[47] Chen, T. C.; Holick, M. F. Vitamin D and prostate cancer prevention and treatment. *Trends. Endocrinol. Metab.*, **2003**, *14*(9), 423-430.

[48] Luscombe, C. J.; Fryer, A. A.; French, M. E.; Liu, S.; Saxby, M. F.; Jones, P. W.; Strange, R. C. Exposure to ultraviolet radiation: association with susceptibility and age at presentation with prostate cancer. *Lancet*, **2001**, *358*(9282), 641-642.

[49] Giovannucci, E.; Liu, Y.; Rimm, E. B.; Hollis, B. W.; Fuchs, C. S.; Stampfer, M. J.; Willett, W. C. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst.*, **2006**, *98*(7), 451-459.

[50] John, E. M.; Schwartz, G. G.; Koo, J.; Van Den Berg, D.; Ingles, S. A. Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. *Cancer Res.*, **2005**, *65*(12), 5470-5479.

[51] John, E. M.; Schwartz, G. G.; Dreon, D. M.; Koo, J. Vitamin D and breast cancer risk: the NHANES I Epidemiologic follow-up study, 1971-1975 to 1992. National Health and Nutrition Examination Survey. *Cancer Epidemiol. Biomarkers Prev.*, **1999**, *8*(5), 399-406.

[52] Porojnicu, A. C.; Robsahm, T. E.; Dahlback, A.; Berg, J. P.; Christiani, D.; Bruland, O. S.; Moan, J. Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role? *Lung Cancer*, **2007**, *55*(3), 263-270.

[53] Robsahm, T. E.; Tretli, S.; Dahlback, A.; Moan, J. Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and

prostate cancer (Norway). *Cancer Causes Control*, **2004**, *15*(2), 149-158.

[54] Garland, C. F.; Mohr, S. B.; Gorham, E. D.; Grant, W. B.; Garland, F. C. Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer. *Am. J. Prev. Med.*, **2006**, *31*(6), 512-514.

[55] Stolzenberg-Solomon, R. Z.; Hayes, R. B.; Horst, R. L.; Anderson, K. E.; Hollis, B. W.; Silverman, D. T. Serum vitamin D and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian screening trial. *Cancer Res.*, **2009**, *69*(4), 1439-1447.

[56] Clemens, T. L.; Adams, J. S.; Henderson, S. L.; Holick, M. F. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. *Lancet*, **1982**, *1*(8263), 74-76.

[57] Garland, C. F.; Gorham, E. D.; Mohr, S. B.; Garland, F. C. Vitamin D for cancer prevention: global perspective. *Ann. Epidemiol.*, **2009**, *19*(7), 468-483.

[58] Yin, L.; Grandi, N.; Raum, E.; Haug, U.; Arndt, V.; Brenner, H. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. *Aliment. Pharmacol. Ther.*, **2009**, *30*(2), 113-125.

[59] Ng, K.; Meyerhardt, J. A.; Wu, K.; Feskanich, D.; Hollis, B. W.; Giovannucci, E. L.; Fuchs, C. S. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. *J. Clin. Oncol.*, **2008**, *26*(18), 2984-2991.

[60] Mezawa, H.; Sugiura, T.; Watanabe, M.; Norizoe, C.; Takahashi, D.; Shimojima, A.; Tamez, S.; Tsutsumi, Y.; Yanaga, K.; Urashima, M. Serum vitamin D levels and survival of patients with colorectal cancer: post-hoc analysis of a prospective cohort study. *BMC Cancer*, **2010**, *10,* 347.

[61] Li, H.; Stampfer, M. J.; Hollis, J. B.; Mucci, L. A.; Gaziano, J. M.; Hunter, D.; Giovannucci, E. L.; Ma, J. A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. *PLoS Med.*, **2007**, *4*(3), e103.

[62] Flanagan, L.; Packman, K.; Juba, B.; O'Neill, S.; Tenniswood, M.; Welsh, J. Efficacy of Vitamin D compounds to modulate estrogen receptor negative breast cancer growth and invasion. *J Steroid Biochem. Mol. Biol.*, **2003**, *84*(2-3), 181-192.

[63] Nakagawa, K.; Kawaura, A.; Kato, S.; Takeda, E.; Okano, T. 1 alpha,25-Dihydroxyvitamin D(3) is a preventive factor in the metastasis of lung cancer. *Carcinogenesis*, **2005**, *26*(2), 429-440.

[64] Yilmaz, M.; Christofori, G. Mechanisms of motility in metastasizing cells. *Mol. Cancer Res.*, **2010**, *8*(5), 629-642.

[65] Angers, S.; Moon, R. T. Proximal events in Wnt signal transduction. *Nat. Rev. Mol. Cell Biol.*, **2009**, *10*(7), 468-477.

[66] Sarkar, F. H.; Li, Y.; Wang, Z.; Kong, D. The role of nutraceuticals in the regulation of Wnt and Hedgehog signaling in cancer. *Cancer Metastasis Rev.*, **2010**, *29*(3), 383-394.

[67] Pendas-Franco, N.; Aguilera, O.; Pereira, F.; Gonzalez-Sancho, J. M.; Munoz, A. Vitamin D and Wnt/beta-catenin pathway in colon cancer: role and regulation of DICKKOPF genes. *Anticancer Res.*, **2008**, *28*(5A), 2613-2623.

[68] Liu, W.; Guo, M.; Ezzat, S.; Asa, S. L. Vitamin D inhibits CEACAM1 to promote insulin/IGF-I receptor signaling without compromising anti-proliferative action. *Lab. Invest.*, **2011**, *91*(1), 147-156.

[69] Sung, V.; Feldman, D. 1,25-Dihydroxyvitamin D3 decreases human prostate cancer cell adhesion and migration. *Mol. Cell Endocrinol.*, **2000**, *164*(1-2), 133-143.

[70] Cheng, J. C.; Klausen, C.; Leung, P. C. Hydrogen peroxide mediates EGF-induced down-regulation of E-cadherin expression via p38 MAPK and snail in human ovarian cancer cells. *Mol. Endocrinol.*, **2010**, *24*(8), 1569-1580.

[71] Tong, W. M.; Hofer, H.; Ellinger, A.; Peterlik, M.; Cross, H. S. Mechanism of antimitogenic action of vitamin D in human colon carcinoma cells: relevance for suppression of epidermal growth factor-stimulated cell growth. *Oncol. Res.*, **1999**, *11*(2), 77-84.

[72] Alvarez-Diaz, S.; Valle, N.; Garcia, J. M.; Pena, C.; Freije, J. M.; Quesada, V.; Astudillo, A.; Bonilla, F.; Lopez-Otin, C.; Munoz, A. Cystatin D is a candidate tumor suppressor gene induced by vitamin D in human colon cancer cells. *J. Clin. Invest.*, **2009**, *119*(8), 2343-2358.

[73] Palmer, H. G.; Sanchez-Carbayo, M.; Ordonez-Moran, P.; Larriba, M. J.; Cordon-Cardo, C.; Munoz, A. Genetic signatures of differentiation induced by 1alpha,25-dihydroxyvitamin D3 in human colon cancer cells. *Cancer Res.*, **2003**, *63*(22), 7799-7806.

[74] Barbachano, A.; Ordonez-Moran, P.; Garcia, J. M.; Sanchez, A.; Pereira, F.; Larriba, M. J.; Martinez, N.; Hernandez, J.; Landolfi, S.; Bonilla, F.; Palmer, H. G.; Rojas, J. M.; Munoz, A. SPROUTY-2 and E-cadherin regulate reciprocally and dictate colon cancer cell tumourigenicity. *Oncogene*, **2010**, *29*(34), 4800-4813.

[75] Pereira, F.; Barbachano, A.; Silva, J.; Bonilla, F.; Campbell, M. J.; Munoz, A.; Larriba, M. J. KDM6B/JMJD3 histone demethylase is induced by vitamin D and modulates its effects in colon cancer cells. *Hum. Mol. Genet.*, **2011**, *20*(23), 4655-4665.

[76] Halder, S. K.; Goodwin, J. S.; Al-Hendy, A. 1,25-Dihydroxyvitamin D3 reduces TGF-beta3-induced fibrosis-related gene expression in human uterine leiomyoma cells. *J. Clin. Endocrinol. Metab.*, **2011**, *96*(4), E754-762.

[77] Pendas-Franco, N.; Gonzalez-Sancho, J. M.; Suarez, Y.; Aguilera, O.; Steinmeyer, A.; Gamallo, C.; Berciano, M. T.; Lafarga, M.; Munoz, A. Vitamin D regulates the phenotype of human breast cancer cells. *Differentiation*, **2007**, *75*(3), 193-207.

[78] Larriba, M. J.; Bonilla, F.; Munoz, A. The transcription factors Snail1 and Snail2 repress vitamin D receptor during colon cancer progression. *J. Steroid Biochem. Mol. Biol.*, **2010**, *121*(1-2), 106-109.

[79] Larriba, M. J.; Martin-Villar, E.; Garcia, J. M.; Pereira, F.; Pena, C.; de Herreros, A. G.; Bonilla, F.; Munoz, A. Snail2 cooperates with Snail1 in the repression of vitamin D receptor in colon cancer. *Carcinogenesis*, **2009**, *30*(8), 1459-1468.

[80] Pena, C.; Garcia, J. M.; Garcia, V.; Silva, J.; Dominguez, G.; Rodriguez, R.; Maximiano, C.; Garcia de Herreros, A.; Munoz, A.; Bonilla, F. The expression levels of the transcriptional regulators p300 and CtBP modulate the correlations between SNAIL, ZEB1, E-cadherin and vitamin D receptor in human colon carcinomas. *Int. J. Cancer*, **2006**, *119*(9), 2098-2104.

[81] Pena, C.; Garcia, J. M.; Larriba, M. J.; Barderas, R.; Gomez, I.; Herrera, M.; Garcia, V.; Silva, J.; Dominguez, G.; Rodriguez, R.; Cuevas, J.; de Herreros, A. G.; Casal, J. I.; Munoz, A.; Bonilla, F. SNAI1 expression in colon cancer related with CDH1 and VDR downregulation in normal adjacent tissue. *Oncogene*, **2009**, *28*(49), 4375-4385.

[82] Sakamoto, S.; Ryan, A. J.; Kyprianou, N. Targeting vasculature in urologic tumors: mechanistic and therapeutic significance. *J. Cell Biochem.*, **2008**, *103*(3), 691-708.

[83] Iiizumi, M.; Liu, W.; Pai, S. K.; Furuta, E.; Watabe, K. Drug development against metastasis-related genes and their pathways: a rationale for cancer therapy. *Biochim. Biophys. Acta.*, **2008**, *1786*(2), 87-104.

[84] Bao, B. Y.; Yeh, S. D.; Lee, Y. F. 1alpha,25-dihydroxyvitamin D3 inhibits prostate cancer cell invasion via modulation of selective proteases. *Carcinogenesis*, **2006**, *27*(1), 32-42.

[85] Koli, K.; Keski-Oja, J. 1alpha,25-dihydroxyvitamin D3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. *Cell Growth Differ.*, **2000**, *11*(4), 221-229.

[86] Nakagawa, K.; Sasaki, Y.; Kato, S.; Kubodera, N.; Okano, T. 22-Oxa-1alpha,25-dihydroxyvitamin D3 inhibits metastasis and angiogenesis in lung cancer. *Carcinogenesis*, **2005**, *26*(6), 1044-1054.

[87] Paduch, R.; Kandefer-Szerszen, M. Vitamin D, tamoxifen and beta-estradiol modulate breast cancer cell growth and interleukin-6 and metalloproteinase-2 production in three-dimensional co-cultures of tumor cell spheroids with endothelium. *Cell Biol. Toxicol.*, **2005**, *21*(5-6), 247-256.

[88] Gonzalez-Sancho, J. M.; Alvarez-Dolado, M.; Munoz, A. 1,25-Dihydroxyvitamin D3 inhibits tenascin-C expression in mammary epithelial cells. *FEBS Lett.*, **1998**, *426*(2), 225-228.

[89] Kisker, O.; Onizuka, S.; Becker, C. M.; Fannon, M.; Flynn, E.; D'Amato, R.; Zetter, B.; Folkman, J.; Ray, R.; Swamy, N.; Pirie-Shepherd, S. Vitamin D binding protein-macrophage activating factor (DBP-maf) inhibits angiogenesis and tumor growth in mice. *Neoplasia*, **2003**, *5*(1), 32-40.

[90] Gregory, K. J.; Zhao, B.; Bielenberg, D. R.; Dridi, S.; Wu, J.; Jiang, W.; Huang, B.; Pirie-Shepherd, S.; Fannon, M. Vitamin D binding protein-macrophage activating factor directly inhibits proliferation, migration, and uPAR expression of prostate cancer cells. *PLoS One*, **2010**, *5*(10), e13428.

[91] Pacini, S.; Punzi, T.; Morucci, G.; Gulisano, M.; Ruggiero, M. Effects of vitamin D-binding protein-derived macrophage-activating factor on human breast cancer cells. *Anticancer Res.*, **2012**, *32*(1), 45-52.

[92] Collins, A. T.; Berry, P. A.; Hyde, C.; Stower, M. J.; Maitland, N. J. Prospective identification of tumorigenic prostate cancer stem cells. *Cancer Res.*, **2005**, *65*(23), 10946-10951.

[93] Li, C.; Heidt, D. G.; Dalerba, P.; Burant, C. F.; Zhang, L.; Adsay, V.; Wicha, M.; Clarke, M. F.; Simeone, D. M. Identification of pancreatic cancer stem cells. *Cancer Res.*, **2007**, *67*(3), 1030-1037.

[94] So, J. Y.; Lee, H. J.; Smolarek, A. K.; Paul, S.; Wang, C. X.; Maehr, H.; Uskokovic, M.; Zheng, X.; Conney, A. H.; Cai, L.; Liu, F.; Suh, N. A novel Gemini vitamin D analog represses the expression of a stem cell marker CD44 in breast cancer. *Mol. Pharmacol.*, **2011**, *79*(3), 360-367.

[95] Xu, H.; Posner, G. H.; Stevenson, M.; Campbell, F. C. Apc(MIN) modulation of vitamin D secosteroid growth control. *Carcinogenesis*, **2010**, *31*(8), 1434-1441.

[96] Ponta, H.; Sherman, L.; Herrlich, P. A. CD44: from adhesion molecules to signalling regulators. *Nat. Rev. Mol. Cell Biol.*, **2003**, *4*(1), 33-45.

[97] Gotte, M.; Yip, G. W. Heparanase, hyaluronan, and CD44 in cancers: a breast carcinoma perspective. *Cancer Res.*, **2006**, *66*(21), 10233-10237.

[98] Khan, S. A.; Cook, A. C.; Kappil, M.; Gunthert, U.; Chambers, A. F.; Tuck, A. B.; Denhardt, D. T. Enhanced cell surface CD44 variant (v6, v9) expression by osteopontin in breast cancer epithelial cells facilitates tumor cell migration: novel post-transcriptional, post-translational regulation. *Clin. Exp. Metastasis*, **2005**, *22*(8), 663-673.

[99] So, J. Y.; Smolarek, A. K.; Salerno, D. M.; Maehr, H.; Uskokovic, M.; Liu, F.; Suh, N. Targeting CD44-STAT3 signaling by Gemini vitamin D analog leads to inhibition of invasion in basal-like breast cancer. *PLoS One*, **2013**, *8*(1), e54020.

[100] Krishnan, A. V.; Shinghal, R.; Raghavachari, N.; Brooks, J. D.; Peehl, D. M.; Feldman, D. Analysis of vitamin D-regulated gene expression in LNCaP human prostate cancer cells using cDNA microarrays. *Prostate*, **2004**, *59*(3), 243-251.

[101] Kurdistani, S. K.; Arizti, P.; Reimer, C. L.; Sugrue, M. M.; Aaronson, S. A.; Lee, S. W. Inhibition of tumor cell growth by RTP/rit42 and its responsiveness to p53 and DNA damage. *Cancer Res.*, **1998**, *58*(19), 4439-4444.

[102] Guan, R. J.; Ford, H. L.; Fu, Y.; Li, Y.; Shaw, L. M.; Pardee, A. B. Drg-1 as a differentiation-related, putative metastatic suppressor gene in human colon cancer. *Cancer Res.*, **2000**, *60*(3), 749-755.

[103] Tumminello, F. M.; Badalamenti, G.; Incorvaia, L.; Fulfaro, F.; D'Amico, C.; Leto, G. Serum interleukin-6 in patients with metastatic bone disease: correlation with cystatin C. *Med. Oncol.*, **2009**, *26*(1), 10-15.

[104] Nonn, L.; Peng, L.; Feldman, D.; Peehl, D. M. Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 5: implications for prostate cancer prevention by vitamin D. *Cancer Res.*, **2006**, *66*(8), 4516-4524.

[105] Abdulghani, J.; Gu, L.; Dagvadorj, A.; Lutz, J.; Leiby, B.; Bonuccelli, G.; Lisanti, M. P.; Zellweger, T.; Alanen, K.; Mirtti, T.; Visakorpi, T.; Bubendorf, L.; Nevalainen, M. T. Stat3 promotes metastatic progression of prostate cancer. *Am. J. Pathol.*, **2008**, *172*(6), 1717-1728.

[106] Grant, W. B. Vitamin D may reduce prostate cancer metastasis by several mechanisms including blocking Stat3. *Am. J. Pathol.*, **2008**, *173*(5), 1589-1590.

[107] Langley, R. R.; Fidler, I. J. The seed and soil hypothesis revisited--the role of tumor-stroma interactions in metastasis to different organs. *Int. J. Cancer*, **2011**, *128*(11), 2527-2535.

[108] Yoneda, T. [Mechanism and strategy for treatment of cancer metastasis to bone]. *Gan. To. Kagaku. Ryoho.*, **2011**, *38*(6), 877-884.

[109] Sasaki, A.; Boyce, B. F.; Story, B.; Wright, K. R.; Chapman, M.; Boyce, R.; Mundy, G. R.; Yoneda, T. Bisphosphonate risedronate reduces metastatic human breast cancer burden in bone in nude mice. *Cancer Res.*, **1995**, *55*(16), 3551-3557.

[110] El Abdaimi, K.; Dion, N.; Papavasiliou, V.; Cardinal, P. E.; Binderup, L.; Goltzman, D.; Ste-Marie, L. G.; Kremer, R. The vitamin D analogue EB 1089 prevents skeletal metastasis and prolongs survival time in nude mice transplanted with human breast cancer cells. *Cancer Res.*, **2000**, *60*(16), 4412-4418.

[111] Ooi, L. L.; Zheng, Y.; Zhou, H.; Trivedi, T.; Conigrave, A. D.; Seibel, M. J.; Dunstan, C. R. Vitamin D deficiency promotes growth of MCF-7 human breast cancer in a rodent model of osteosclerotic bone metastasis. *Bone*, **2010**, *47*(4), 795-803.

[112] Zheng, Y.; Zhou, H.; Ooi, L. L.; Snir, A. D.; Dunstan, C. R.; Seibel, M. J. Vitamin D deficiency promotes prostate cancer growth in bone. *Prostate*, **2011**, *71*(9), 1012-1021.

[113] Bhatia, V.; Saini, M. K.; Shen, X.; Bi, L. X.; Qiu, S.; Weigel, N. L.; Falzon, M. EB1089 inhibits the parathyroid hormone-related protein-enhanced bone metastasis and xenograft growth of human prostate cancer cells. *Mol. Cancer Ther.*, **2009**, *8*(7), 1787-1798.

[114] Bikfalvi, A. Angiogenesis and invasion in cancer. *Handb. Clin. Neurol.*, **2012**, *104,* 35-43.

[115] Chung, I.; Wong, M. K.; Flynn, G.; Yu, W. D.; Johnson, C. S.; Trump, D. L. Differential antiproliferative effects of calcitriol on tumor-derived and matrigel-derived endothelial cells. *Cancer Res.*, **2006**, *66*(17), 8565-8573.

[116] Flynn, G.; Chung, I.; Yu, W. D.; Romano, M.; Modzelewski, R. A.; Johnson, C. S.; Trump, D. L. Calcitriol (1,25-dihydroxycholecalciferol) selectively inhibits proliferation of freshly isolated tumor-derived endothelial cells and induces apoptosis. *Oncology*, **2006**, *70*(6), 447-457.

[117] Chung, I.; Karpf, A. R.; Muindi, J. R.; Conroy, J. M.; Nowak, N. J.; Johnson, C. S.; Trump, D. L. Epigenetic silencing of CYP24 in tumor-derived endothelial cells contributes to selective growth inhibition by calcitriol. *J. Biol. Chem.*, **2007**, *282*(12), 8704-8714.

[118] Hill, S. A.; Chaplin, D. J. Detection of microregional fluctuations in erythrocyte flow using laser Doppler microprobes. *Adv. Exp. Med. Biol.*, **1996**, *388,* 367-371.

[119] Couvelard, A.; O'Toole, D.; Turley, H.; Leek, R.; Sauvanet, A.; Degott, C.; Ruszniewski, P.; Belghiti, J.; Harris, A. L.; Gatter, K.; Pezzella, F. Microvascular density and hypoxia-inducible factor pathway in pancreatic endocrine tumours: negative correlation of microvascular density and VEGF expression with tumour progression. *Br. J. Cancer*, **2005**, *92* (1), 94-101.

[120] Semenza, G. L. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer*, **2003**, *3* (10), 721-732.

[121] Papetti, M.; Herman, I. M. Mechanisms of normal and tumor-derived angiogenesis. *Am. J. Physiol. Cell Physiol.*, **2002**, *282*(5), C947-970.

[122] Ben-Shoshan, M.; Amir, S.; Dang, D. T.; Dang, L. H.; Weisman, Y.; Mabjeesh, N. J. 1alpha,25-dihydroxyvitamin D3 (Calcitriol) inhibits hypoxia-inducible factor-1/vascular endothelial growth factor pathway in human cancer cells. *Mol. Cancer Ther.*, **2007**, *6*(4), 1433-1439.

[123] Mantell, D. J.; Owens, P. E.; Bundred, N. J.; Mawer, E. B.; Canfield, A. E. 1 alpha,25-dihydroxyvitamin D(3) inhibits angiogenesis *in vitro* and *in vivo*. *Circ. Res.*, **2000**, *87*(3), 214-220.

[124] Maisonpierre, P. C.; Suri, C.; Jones, P. F.; Bartunkova, S.; Wiegand, S. J.; Radziejewski, C.; Compton, D.; McClain, J.; Aldrich, T. H.; Papadopoulos, N.; Daly, T. J.; Davis, S.; Sato, T. N.; Yancopoulos, G. D. Angiopoietin-2, a natural antagonist for Tie2 that disrupts *in vivo* angiogenesis. *Science*, **1997**, *277*(5322), 55-60.

[125] Metheny-Barlow, L. J.; Li, L. Y. The enigmatic role of angiopoietin-1 in tumor angiogenesis. *Cell Res.*, **2003**, *13* (5), 309-317.

[126] Chakraborti, C. K. Vitamin D as a promising anticancer agent. *Indian J. Pharmacol.*, **2011**, *43*(2), 113-120.

[127] Bernardi, R. J.; Johnson, C. S.; Modzelewski, R. A.; Trump, D. L. Antiproliferative effects of 1alpha,25-dihydroxyvitamin D(3) and vitamin D analogs on tumor-derived endothelial cells. *Endocrinology*, **2002**, *143*(7), 2508-2514.

[128] Sun, W.; Xie, H.; Ji, J.; Zhou, X.; Goltzman, D.; Miao, D. Defective female reproductive function in 1,25(OH)2D-deficient mice results from indirect effect mediated by extracellular calcium and/or phosphorus. *Am. J. Physiol. Endocrinol. Metab.*, **2010**, *299*(6), E928-935.

[129] Fernandez-Garcia, N. I.; Palmer, H. G.; Garcia, M.; Gonzalez-Martin, A.; del Rio, M.; Barettino, D.; Volpert, O.; Munoz, A.; Jimenez, B. 1alpha,25-Dihydroxyvitamin D3 regulates the expression of Id1 and Id2 genes and the angiogenic phenotype of human colon carcinoma cells. *Oncogene*, **2005**, *24*(43), 6533-6544.

[130] Suh, J.; Rabson, A. B. NF-kappaB activation in human prostate cancer: important mediator or epiphenomenon? *J. Cell Biochem.*, **2004**, *91*(1), 100-117.

[131] Koch, A. E.; Polverini, P. J.; Kunkel, S. L.; Harlow, L. A.; DiPietro, L. A.; Elner, V. M.; Elner, S. G.; Strieter, R. M.

Interleukin-8 as a macrophage-derived mediator of angiogenesis. *Science*, **1992**, *258*(5089), 1798-1801.

[132] Krishnan, A. V.; Feldman, D. Molecular pathways mediating the anti-inflammatory effects of calcitriol: implications for prostate cancer chemoprevention and treatment. *Endocr. Relat. Cancer*, **2010**, *17*(1), R19-38.

[133] Tse, A. K.; Zhu, G. Y.; Wan, C. K.; Shen, X. L.; Yu, Z. L.; Fong, W. F. 1alpha,25-Dihydroxyvitamin D3 inhibits transcriptional potential of nuclear factor kappa B in breast cancer cells. *Mol. Immunol.*, **2010**, *47*(9), 1728-1738.

[134] Bao, B. Y.; Yao, J.; Lee, Y. F. 1alpha, 25-dihydroxyvitamin D3 suppresses interleukin-8-mediated prostate cancer cell angiogenesis. *Carcinogenesis*, **2006**, *27*(9), 1883-1893.

[135] Grant, D. S.; Kleinman, H. K.; Goldberg, I. D.; Bhargava, M. M.; Nickoloff, B. J.; Kinsella, J. L.; Polverini, P.; Rosen, E. M. Scatter factor induces blood vessel formation *in vivo*. *Proc. Natl. Acad. Sci. U S A*, **1993**, *90*(5), 1937-1941.

[136] Chattopadhyay, N.; MacLeod, R. J.; Tfelt-Hansen, J.; Brown, E. M. 1alpha,25(OH)2-vitamin D3 inhibits HGF synthesis and secretion from MG-63 human osteosarcoma cells. *Am. J. Physiol. Endocrinol. Metab.*, **2003**, *284*(1), E219-227.

[137] Jogie-Brahim, S.; Feldman, D.; Oh, Y. Unraveling insulin-like growth factor binding protein-3 actions in human disease. *Endocr. Rev.*, **2009**, *30*(5), 417-437.

[138] Kim, J. H.; Choi, D. S.; Lee, O. H.; Oh, S. H.; Lippman, S. M.; Lee, H. Y. Antiangiogenic antitumor activities of IGFBP-3 are mediated by IGF-independent suppression of Erk1/2 activation and Egr-1-mediated transcriptional events. *Blood*, **2011**, *118*(9), 2622-2631.

[139] Garonna, E.; Botham, K. M.; Birdsey, G. M.; Randi, A. M.; Gonzalez-Perez, R. R.; Wheeler-Jones, C. P. Vascular endothelial growth factor receptor-2 couples cyclo-oxygenase-2 with pro-angiogenic actions of leptin on human endothelial cells. *PLoS One*, **2011**, *6*(4), e18823.

[140] Konno, H.; Baba, M.; Shoji, T.; Ohta, M.; Suzuki, S.; Nakamura, S. Cyclooxygenase-2 expression correlates with uPAR levels and is responsible for poor prognosis of colorectal cancer. *Clin. Exp. Metastasis*, **2002**, *19*(6), 527-534.

[141] Yamauchi, T.; Watanabe, M.; Kubota, T.; Hasegawa, H.; Ishii, Y.; Endo, T.; Kabeshima, Y.; Yorozuya, K.; Yamamoto, K.; Mukai, M.; Kitajima, M. Cyclooxygenase-2 expression as a new marker for patients with colorectal cancer. *Dis. Colon Rectum*, **2002**, *45*(1), 98-103.

[142] Chang, S. H.; Liu, C. H.; Conway, R.; Han, D. K.; Nithipatikom, K.; Trifan, O. C.; Lane, T. F.; Hla, T. Role of prostaglandin E2-dependent angiogenic switch in cyclooxygenase 2-induced breast cancer progression. *Proc. Natl. Acad. Sci. U S A*, **2004**, *101*(2), 591-596.

[143] Fukuda, R.; Kelly, B.; Semenza, G. L. Vascular endothelial growth factor gene expression in colon cancer cells exposed to prostaglandin E2 is mediated by hypoxia-inducible factor 1. *Cancer Res.*, **2003**, *63*(9), 2330-2334.

[144] Na, H. K.; Park, J. M.; Lee, H. G.; Lee, H. N.; Myung, S. J.; Surh, Y. J. 15-Hydroxyprostaglandin dehydrogenase as a novel molecular target for cancer chemoprevention and therapy. *Biochem. Pharmacol.*, **2011**, *82*(10), 1352-1360.

[145] Huang, G.; Eisenberg, R.; Yan, M.; Monti, S.; Lawrence, E.; Fu, P.; Walbroehl, J.; Lowenberg, E.; Golub, T.; Merchan, J.; Tenen, D. G.; Markowitz, S. D.; Halmos, B. 15-Hydroxyprostaglandin dehydrogenase is a target of hepatocyte nuclear factor 3beta and a tumor suppressor in lung cancer. *Cancer Res.*, **2008**, *68*(13), 5040-5048.

[146] Song, H. J.; Myung, S. J.; Kim, I. W.; Jeong, J. Y.; Park, Y. S.; Lee, S. M.; Nam, W. H.; Ryu, Y. M.; Fink, S. P.; Yang, D. H.; Jung, H. Y.; Kim, J. H. 15-hydroxyprostaglandin dehydrogenase is downregulated and exhibits tumor suppressor activity in gastric cancer. *Cancer Invest.*, **2011**, *29*(4), 257-265.

[147] Wolf, I.; O'Kelly, J.; Rubinek, T.; Tong, M.; Nguyen, A.; Lin, B. T.; Tai, H. H.; Karlan, B. Y.; Koeffler, H. P. 15-hydroxyprostaglandin dehydrogenase is a tumor suppressor of human breast cancer. *Cancer Res.*, **2006**, *66*(15), 7818-7823.

[148] Yan, M.; Rerko, R. M.; Platzer, P.; Dawson, D.; Willis, J.; Tong, M.; Lawrence, E.; Lutterbaugh, J.; Lu, S.; Willson, J. K.; Luo, G.; Hensold, J.; Tai, H. H.; Wilson, K.; Markowitz, S. D. 15-Hydroxyprostaglandin dehydrogenase, a COX-2 oncogene antagonist, is a TGF-beta-induced suppressor of human gastrointestinal cancers. *Proc. Natl. Acad. Sci. U S A*, **2004**, *101*(50), 17468-17473.

[149] Moreno, J.; Krishnan, A. V.; Swami, S.; Nonn, L.; Peehl, D. M.; Feldman, D. Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cells. *Cancer Res.*, **2005**, *65*(17), 7917-7925.

[150] Swami, S.; Krishnan, A. V.; Moreno, J.; Bhattacharyya, R. B.; Peehl, D. M.; Feldman, D. Calcitriol and genistein actions to inhibit the prostaglandin pathway: potential combination therapy to treat prostate cancer. *J. Nutr.*, **2007**, *137*(1 Suppl), 205S-210S.

[151] Clinckspoor, I.; Verlinden, L.; Overbergh, L.; Korch, C.; Bouillon, R.; Mathieu, C.; Verstuyf, A.; Decallonne, B. 1,25-dihydroxyvitamin D3 and a superagonistic analog in combination with paclitaxel or suberoylanilide hydroxamic acid have potent antiproliferative effects on anaplastic thyroid cancer. *J. Steroid Biochem. Mol. Biol.*, **2011**, *124*(1-2), 1-9.

[152] Kulkarni, A. D.; van Ginkel, P. R.; Darjatmoko, S. R.; Lindstrom, M. J.; Albert, D. M. Use of combination therapy with cisplatin and calcitriol in the treatment of Y-79 human retinoblastoma xenograft model. *Br. J. Ophthalmol.*, **2009**, *93*(8), 1105-1108.

[153] Ma, Y.; Yu, W. D.; Trump, D. L.; Johnson, C. S. 1,25D3 enhances antitumor activity of gemcitabine and cisplatin in human bladder cancer models. *Cancer*, **2010**, *116*(13), 3294-3303.

[154] Rassnick, K. M.; Muindi, J. R.; Johnson, C. S.; Balkman, C. E.; Ramnath, N.; Yu, W. D.; Engler, K. L.; Page, R. L.; Trump, D. L. *In vitro* and *in vivo* evaluation of combined calcitriol and cisplatin in dogs with spontaneously occurring tumors. *Cancer Chemother. Pharmacol.*, **2008**, *62*(5), 881-891.

[155] Fakih, M. G.; Trump, D. L.; Muindi, J. R.; Black, J. D.; Bernardi, R. J.; Creaven, P. J.; Schwartz, J.; Brattain, M. G.; Hutson, A.; French, R.; Johnson, C. S. A phase I pharmacokinetic and pharmacodynamic study of intravenous calcitriol in combination with oral gefitinib in patients with advanced solid tumors. *Clin. Cancer Res.*, **2007**, *13*(4), 1216-1223.

[156] Muindi, J. R.; Peng, Y.; Potter, D. M.; Hershberger, P. A.; Tauch, J. S.; Capozzoli, M. J.; Egorin, M. J.; Johnson, C. S.; Trump, D. L. Pharmacokinetics of high-dose oral calcitriol: results from a phase 1 trial of calcitriol and paclitaxel. *Clin. Pharmacol. Ther.*, **2002**, *72*(6), 648-659.

[157] Beer, T. M.; Garzotto, M.; Katovic, N. M. High-dose calcitriol and carboplatin in metastatic androgen-independent prostate cancer. *Am. J. Clin. Oncol.*, **2004**, *27*(5), 535-541.

[158] Beer, T. M.; Ryan, C. W.; Venner, P. M.; Petrylak, D. P.; Chatta, G. S.; Ruether, J. D.; Redfern, C. H.; Fehrenbacher, L.; Saleh, M. N.; Waterhouse, D. M.; Carducci, M. A.; Vicario, D.; Dreicer, R.; Higano, C. S.; Ahmann, F. R.; Chi, K. N.; Henner, W. D.; Arroyo, A.; Clow, F. W. Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. *J. Clin. Oncol.*, **2007**, *25*(6), 669-674.

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