Chapter 18

The Impact of Vitamin D in Cancer

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1. Introduction

The relationship between vitamin D and cancer has previously been reported in the literature. A systemic review and meta-analysis of prospective cohort studies revealed that a 20 nmol/L increase in the 25-hydroxyvitamin D_3 (25OHD) levels was associated with an 8% lower mortality in the elderly population (Schöttker et al., 2012). Oncology patients had significantly lower mean serum vitamin D levels than non-cancer primary care patients from the same geographic region (Churilla et al., 2011). In a community oncology experience, vitamin D deficiency is widespread in cancer patients and correlates with advanced stage disease (Churilla et al., 2012). A high prevalent of vitamin D deficiency has been associated with head and neck cancer (Orell-Kotikangas et al., 2011), breast cancer (Crew et al., 2009; Peppone et al., 2012), vulvar cancer (Salehin et al., 2012), prostate cancer (Varsavsky et al., 2011), pancreatic cancer (Wolpin et al., 2011), gastric cancer (Ren et al., 2012), colon and rectal cancer (Tangrea et al., 1997), ovarian cancer (Lefkowitz et al., 1994), oral cavity and esophagus cancers (Lipworth et al., 2009), myelo-proliferative neoplasms and myelo-dysplastic syndromes (Pardanani et al., 2011), multiple myeloma (Ng et at., 2009), non-Hodgkin's lymphoma (Drake et al., 2010), and chronic lymphocytic leukemia (Shamafelt et al., 2011). On the other hand, a serum 25OHD concentration of 25 nmol/L was associated with a 17% reduction in incidence of cancer, a 29% reduction in total cancer mortality, and a 45% reduction in digestive system cancer mortality (Giovannucci et al., 2006). Improving vitamin D status may also help lower the risk of colorectal cancer (Wu et al., 2011a). In a case-control study, a higher vitamin D intake is associated with a lower risk of esophageal squamous cell carcinoma (Launoy et al., 1998). A meta-analysis revealed that an increase of serum 25OHD by 50 nmol/L was associated with a risk reduction of 59% for rectal cancer and 22% for colon cancer (Yin et al., 2009). High 25OHD levels were associated with better prognosis in breast, colon, prostate cancer, and lung cancer relative to patients with lower 25OHD levels (Robsahm et al., 2004; Zhou et al., 2007). In a murine model, dietary vitamin D may play an important role as a preventive agent in androgen-insensitive human prostate tumor growth (Ray et al., 2012). The season in which patients were operated on seemed to have an effect on survival of patients undergoing resection of non-small cell lung cancer (Turna et al., 2012). The survival of patients who had surgery in winter was statistically significantly shorter than that of patients who underwent surgery in the summer. In Australia, prostate cancer mortality rates are inversely correlated with solar radiation exposure (Loke et al., 2011). Dietary vitamin D_3 and calcitriol have been shown to demonstrate equivalent anticancer activity in mouse xenograft models of breast and prostate cancers (Swani et al., 2012). The combination of calcitriol and dietary soy resulted in substantially greater inhibition of tumor growth than the inhibition achieved with either agent alone in a mouse xenograft model of prostate cancer (Wang et al., 2012a). Soy diets alone caused a modest elevation in serum calcitriol. Vitamin D_3 treatment significantly suppressed the viability of gastric cancer and cholangiocarcinoma cells and also had a synergistic effect with other anti-cancer drugs, such as paclitaxel, adriamycin, and vinblastine (Baek et al., 2011). The vitamin D analog, 19-Nor-2α-(3-hydroxypropyl)-1α,25-dihydroxyvitamin D_3, is a potent cell growth regulator with enhanced chemotherapeutic potency in liver cancer cells (Chiang et al., 2011). Alphacalcidol, a vitamin D analogue, has been demonstrated significant antitumor activity in patients with low-grade non-Hodgkin's lymphoma of the follicular, small-cleaved cell type (Raina et al., 1991). In patient with parathyroid cancer, vitamin D has been shown to prevent or delay the progression of recurrence (Palmieri-Sevier et al., 1993). In locally advanced or cutaneous metastatic breast cancer, topical calcipotriol treatment reduced the diameter of treated lesions that contained vitamin D receptor (*VDR*) (Bower et al., 1991). In a clinical trial, high-dose calcitriol decreased prostatic-specific antigen (PSA) levels by 50% and reduced thrombosis in prostate cancer patients (Beer et al., 2003 & 2006). In hepatocellular carcinoma, calcitriol and its analogs have been reported to reduce tumor volume, increase hepatocarcinoma cell apoptosis by 21.4%, and transient stabilize serum alpha-fetoprotein levels (Dalhoff et al., 2003; Luo et al., 2004; Morris et al., 2002). These findings suggested a relationship between vitamin D and cancer. In this chapter, we will discuss the role of vitamin D in cancer.

2. Genetic factors related to vitamin D and cancer

2.1. The Major Histocompatibility Complex (MHC) class II molecules

The major histocompatibility complex (MHC) class II molecules play an important role in the immune system and are essential in the defense against infection. The human MHC class II molecules are encoded by three different human leukocytic antigen (HLA) isotypes: HLA-DR, -DQ, and -DP. Studies have suggested that several genes within MHC region promote cancer susceptibility. A chimeric DR4 homozygous transgenic mouse line is reported to spontaneously develop diverse hematological malignancies at a high frequency (Raffegerst et al., 2009). Most of these neoplasms were highly similar to those found in human diseases. HLA-DR antigen expression was correlated with the histopathological type and to the degree of cell differentiation in cutaneous squamous cell carcinomas (Garcia-Plata et al., 1993). The DRB1*03 and DR-B1*13 alleles were significantly more frequent in patients with nasopharyngeal carcinoma compared with controls in southern Tunisia (Makni et al., 2010). The DR1 gene is

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strongly associated with thyroid carcinoma (Panza et al., 1982). The HLA-DR was also increased in poorly differentiated thyroid carcinoma, especially in the anaplastic type (Lindhorst et al., 2002). The DQA1*0102 and DPB1*0501 alleles were significantly more common in Chinese patients with hepatocellular carcinoma (HCC) (Donaldson et al., 2001). The frequency of DRB1*0404 allele was significantly higher in the gastric cancer group compared with the gastritis group in Koreans (Lee et al., 2009). However, the frequencies of the DRB1*0405 and DQB1*0401 alleles were increased in the Japanese patients with intestinal-type gastric cancer compared with controls (Ando et al., 2009). Somatic mutations affecting HLA class II genes may lead to loss of HLA class II expression due to the formation of microsatellites in unstable colorectal carcinomas (Michel et al., 2010). The DRB1*15 allele and the haplotype DRB1*15 DQB1*0602 were associated with human papillomavirus (HPV)-16 positive invasive cervical cancer in Mexican women (Hernández-Hernández et al., 2009). The DRB1*0410 allele was the susceptibility allele in Japanese patients with testicular germ cell carcinoma (Ozdemir et al., 1997). Furthermore, the frequencies of the DRB1*09 and DQB1*03 alleles were increased in patients with non-Hodgkin's lymphoma and diffuse large B cell lymphoma compared with normal controls (Choi et al., 2008). The frequencies of the DRB1*04 and DRB1*15 alleles were significantly higher in Turkish children with acute leukemia compared with controls (Ozdilli et al., 2010). The DRB1*16 allele was a marker for a signignificant risk of chronic myelogenous leukemia in Eastern Canada (Naugler and Liwski, 2009). The DRB1*04 and DRB5 alleles are associated with disease progression in Iranian patients with chronic lymphocytic leukemia (Hojattat-Farsangi et al., 2008). On the other hand, calcitriol is known to stimulate phagocytosis and suppress MHC class II antigen expression in human mononuclear phagocytes (Tokuda et al., 1992 & 1996), thereby preventing antigen-specific T cell proliferation. In addition, calcitriol exerts effects that opposes the effect of IL-4 on MHC class II antigen expression in human monocytes (Xu et al., 1993) and specifically modulates human monocyte phenotype and function by altering HLA-DR antigen expression and antigen presentation, while leaving lytic function intact (Rigby et al., 1990). Calcitriol also decreases interferon-γ-induced HLA-DR antigen expression in normal and transformed human keratinocytes (Tamaki et al., 1990-1991 & Tone et al., 1991) and reduces the levels of HLA-DR mRNA in cultured epithelial tumor cell lines (Tone et al., 1993). In addition, 1α-calcidol significantly modulates the expression of HLA-DR in human peripheral blood monocytes (Scherberich et al., 2005). These findings suggest that calcitriol may have an effect on cancer by suppressing the expression of MHC class II antigens.

2.2. Vitamin D Receptor (VDR)

The expression of VDR in a variety of cell lines, coupled with increased evidence of *VDR* involvement in cell differentiation, inhibition of cellular proliferation and angiogenesis in many tumor types, suggest that vitamin D plays a role in cancer (Luong and Nguyen, 2010 & Lương and Nguyễn, 2012). VDR ablation is associated with ductal ectasia of the primary mammary ducts, loss of secondary and tertiary branches and atrophy of the mammary fad pad (Welsh et al., 2011). Breast cancer patients with high VDR expression showed significant better in progression-free survival and overall survival than patients with moderate/negative VDR expression scores (Ditch et al., 2012). Certain allelic variations in the *VDR* may also be genetic risk factors for developing tumors. There are five important common polymorphisms within the *VDR* gene region that are likely to exert functional effects on *VDR* expression. The anti-carcinogenic potential of vitamin D might be mediated by VDR expression. The association between plasma 25OHD levels and colorectal adenoma was modified by the *Taq*I polymorphism of the VDR gene (Yamaji et al., 2011). There is a significant association between single nucleotide polymorphisms (SNPs) in the VDR gene and vitamin D intake in African Americans with colorectal cancer (Kupfer et al., 2011). The *Bsm*I polymorphism of the VDR gene also modified the association between dietary vitamin D intake and breast cancer (Rollison et al., 2012). The *AA* genotype of VDR is reported to be associated with colorectal cancer, with a stronger association in female patients (Mahmoudi et al., 2012). The *Fok*I and *Bsm*I genotypes of VDR gene are implicated in the pathogenesis of renal cell carcinoma (RCC) in a North Indian population (Arjumand et al., 2012). Altered VDR expression was associated with RCC carcinogenesis via the expression of epithelial Ca^{2+} channel transient receptor potential vanilloid subfamily 5 and 6 (TRPV5/6) (Wu et al., 2011b). There is a significant association between shorter progression-free survival time in patients with head and neck squamous cell carcinoma and the *Fok*I *TT* genotype, as well as the *Cdx2*-*Fox*I-*Apa*I haplotype (Hama et al., 2011). In Spanish children, osteosarcoma patients showed a significantly higher frequency of the *Ff* genotype of the *Fok*I *VDR* gene than the control group (Ruza et al., 2003). In a German population, the *AaTtBb* genotype of the VDR gene is associated with basal cell carcinoma risk, whereas the *aaTTbb* genotype is found at a high frequency in both basal cell carcinomas and cutaneous squamous cell carcinomas compared with controls (Köststner et al., 2012). In a systematic review, *Taq*I, *Bsm*I and *Fok*I polymorphisms of the VDR gene were found to be associated with malignant melanoma (Denzer et al., 2011). Furthermore, the presence of specific VDR *Bsm*I and *Taq*I alleles was associated with a higher C-reactive protein (CRP) level in cancer patients with cachectic syndrome (Punzi et al., 2012). In another prospective study, plasma 25OHD levels and common variation among several vitamin D-related genes (*CYP27A1*, *CYP2R1*, *CYP27B1*, *CYP24A1*, *GC*, *RXRA*, and *VDR*) were associated with lethal prostate cancer risk (Shui et al., 2012). Slattery et al. (2009) examined genetic variants that are linked to the pathway that contribute to colon cancer. They revealed that *Fox*I *VDR* polymorphism was associated with CpG Island methylator phenotype (CIMP) positive/Ki-ras mutated tumors, whereas the Poly *A* and *Cdx2 VDR* polymorphisms were associated only with Ki-ras mutated tumors.

2.3. MicroRNA (miRNA)

MiRNAs are endogenous noncoding RNAs that regulate gene expression through the translational repression or degradation of target mRNA (Bartel, 2004). Aberrant miRNA expression has been well characterized in cancer (Lu et al., 2005). Circulating miRNAs are suggested to be diagnostic and prognostic markers in breast cancer (Cortez et al., 2012). Circulating miRNA-125b expression is associated with chemotherapeutic resistance of breast cancer (Wang et al., 2012b). Several miRNAs are found to share 125b complementarity with a sequence in the 3'-unstranslated region of human VDR mRNA. The overexpression miRNA-125b significantly decreased the endogenous VDR protein level in human breast adenocarcinoma cells lines (MCF-7) to 40% of the control (Mohri et al., 2009). This miRNA is down-regulated in cancer tissue and causes high CYP24 protein expression, which catalyzes the inactivation of calcitriol (Komagata et al., 2009). Stress induced by serum starvation caused significant alteration in the expression of multiple miRNAs including miRNA-182, but calcitriol effectively reversed this alteration in breast epithelial cells (Peng et al., 2010). Vitamin D_3 up-regulated protein 1 (VDUP1) is regulated by miRNA-17-5p at the post-transcriptional levels in senescent fibroblasts (Zhuo et al., 2010). VDUP1 expression is increased in cancer cells (Takahashi et al., 2002; Dutta et al., 2005). In melanoma cell lines, the endogenous VDR mRNA level is inversely associated with expression of miRNA-125b (Essa et al., 2010), and calcitriol also reduced the miRNA-27b expression in these cell lines. In human colon cells, calcitriol induced miRNA-22 and may contribute to its antitumor action against this neoplasm (Alvarez-Diaz et al., 2012). Fifteen miRNAs are also differentially regulated by calcitriol in prostate cancer cells (LNCaP) (Wang et al 2011a). Furthermore, calcitriol regulated miRNA-32 and miRNA-181 expressions in human myeloid leukemia cells (Gocek et al., 2011; Zimmerman et al., 2011; Wang et al., 2009a).

2.4. Renin-Angiotensin System (RAS)

The primary function of the renin-angiotensin system (RAS) is to maintain fluid homeostasis and regulate blood pressure. The angiotensin converting enzyme (ACE) is a key enzyme in the RAS and converts angiotensin (AT) I to the potent vasoconstrictor AT II (Johnston, 1994). The local RAS may influence tissue angiogenesis, cellular proliferation, apoptosis, and inflammation (Deshayes and Nahmias, 2005). Epidemiological and experimental studies suggested that the RAS may contribute to the paracrine regulation of tumor growth. The renin levels are elevated in patients with liver cirrhosis and HCC and positively correlated with α-fetoprotein (Lotfy et al., 2010). The over-expression of ACE is reported in extrahepatic cholangiocarcinoma (Beyazit et al., 2011), leukemic myeloid blast cells (Aksu et al., 2006), and macrophages in the lymph nodes of Hodgkin's disease patients (Koca et al., 2007). The AT II receptors were also expressed in all human gastric cancer lines (Huang et al., 2008), pre-malignant and malignant prostate cells (Louis et al., 2007), human lung cancer xenografts (Feng et al., 2011a), and ovarian cancer (Ino et al., 2006). The RAS mutation in codon 61 was the most common genetic alteration in poorly differentiated thyroid carcinomas (Volante et al., 2009). The ACE *I/D* polymorphism is a possible target for developing genetic markers for breast cancer in Brazilian women (Alves Corrêa et al., 2009). The ACE *I/D* polymorphisms play an important role in breast cancer risk and disease-free survival in Caucasian postmenopausal women (González-Zuloeta Ladd et al., 2012). Carriers of the high-activity *DD* genotype had an increased risk of breast cancer compared with low activity *II/ID* genotype carriers (van der Knaap et al., 2008). The *DD* genotype was associated with patients with an aggressive stage of prostate cancer (Wang et al., 2011b). ACE2 expression was decreased in non-small-cell lung cancer and pancreatic ductal adenocarcinoma in which AT II levels were higher than those in controls (Feng et al., 2010; Zhou et al., 2009). ACE2 has been suggested as a potential molecular target for pancreatic cancer therapy (Zhou et al., 2011). The AT II concentration in gastric cancer region was significantly higher than those of normal region (Kinoshita et al., 2009). Furthermore, AT II receptor blockers (ARB) suppress the cell proliferation effects of AT II in breast cancer cells (Du et al., 2012). The addition of ACE inhibitor or ARB to platinum-based first line chemotherapy contributed to prolong survival in patients with advanced lung cancer (Wilop et al., 2009) and affected the prognosis of advanced pancreatic cancer patients receiving gemcitabine (Nakai et al., 2010). The RAS inhibitors also improved the outcome of sunitinib treatment in metastatic renal cell carcinoma (Keizman et al., 2011). On the other hand, the administration of ACE inhibitors in patients with the ACE *DD* genotype has been shown to decrease the level of calcitriol required (Pérez-Castrillón et al., 2006). In a hypertensive Turkish population, the presence of the ACE *D* allele, which correlates negatively with serum 25OHD levels, is linked to a higher left ventricular mass index value and elevated ambulatory blood pressure measurements (Kulah et al., 2007). In addition, genetic disruption of the *VDR* gene resulted in overstimulation of the RAS with increased renin and angiotensin II production, which lead to high blood pressure and cardiac hypertrophy. However, treatment with captopril reduced cardiac hypertrophy in VDR-knockout mice (Xiang et al., 2005), suggesting that calcitriol may function as an endocrine suppressor of renin biosynthesis. Moreover, calcitriol suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin core promoter (Yuan et al., 2007) and decreases ACE activity in bovine endothelial cells (Higiwara et al., 1988).

2.5. Toll-Like Receptor (TLR)

Toll-like receptors (TLRs) are a group of glycoproteins that functions as surface trans-membrane receptors and are involved in the innate immune responses to exogenous pathogenic microorganisms. Substantial evidence exists for an important role of TLRs in the pathogenesis and outcomes of cancer. TLR2 expression was significantly higher in sporadic colorectal cancerous tissue than in non-cancerous tissue (Nihon-Yanagi et al., 2012). The TLR5 play an important role in tumor progression of gastric cancer (Song et al., 2011). The TLR7 and TLR9 showed high expression in laryngeal carcinoma cells (Shikora et al., 2010). The over-expression of TLR9 was reported oral squamous cell carcinoma (Min et al., 2011), esophageal squamous cell carcinoma (Takala et al., 2011), and breast cancer cells (Qiu et al., 2011; Sandholm et al., 2012). The expression levels of TLR1, TLR2, TLR4, TLR5, TLR6, TLR8, and TLR10 are significantly higher in the human renal carcinoma cell line (780-6) than those in normal renal cell (HK-2) line (Yu et al., 2011). Chronic lymphocytic leukemia cells express all TLRs expressed by normal activated B cells, with a high expression of TLR9 and CD180 and an intermediate expression of TLR1, TLR6, and TLR10 (Arvaniti et al., 2011). The TLR4 polymorphisms are reported in patients with the risk of prostate cancer (Kim et al., 2012), head and neck squamous cell carcinomas (Bergmann et al., 2011), HCC (Minmin et al., 2011), and colon cancer (Eyking et al., 2011). Furthermore, multiple SNPs in TLR2 and TLR4 were associated with colon cancer survival (Slattery et al., 2012). On the other hand, vitamin D deficiency increases the expression of hepatic mRNA levels of TLR2, TLR4, and TLR9 in obese rats (Roth et al., 2011). However, calcitriol suppresses the expression of TLR2 and TLR4 protein and mRNA in human monocytes and triggers hypo-responsiveness to pathogen-associated molecular patterns (Sadeghi et al., 2006). Calcitriol has also been shown to down-regulate intracellular TLR2, TLR4 and TLR 9 expression in human monocytes (Dickie et al., 2010). TLR activation results in the expression of the VDR and 1α-vitamin D hydroxylase in human monocytes (Liu et al., 2006). Additionally, calcitriol can cause the vitamin D-induced expression of cathelicidin in bronchial epithelial cells (Yim et al., 2007) and may enhance the production of cathelicidin LL-37 (Rivas-Santiago et al., 2008). The addition of a VDR antagonist has also

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been shown to inhibit the induction of cathelicidin mRNA by more than 80%, thereby reducing the protein expression of this antimicrobial agent by approximately 70% (Yim et al., 2007). Cathelicidin was abundant in tumor-infiltrating NK1.1$^+$ cells in mice. Cathelicidin knockout mice (*Camp*$^{-/-}$) permitted faster tumor growth than wild type controls; NK cells derived from *Camp*$^{-/-}$ mice showed impaired cytotoxic activity toward tumor targets compared with wild-type mice (Büchau et al., 2010). The human cathelicidin LL-37, which inhibits gastric cancer cell proliferation, is down-regulated in gastric adenocarcinomas (Wu et al., 2010). Gastrointestinal cancer cells lacked LL-37 expression; Cathelicidin expression is modulated by histone-deacetylase (HDAC) inhibitors in various gastrointestinal cells, including gastric and hepatocellular cells (Schauer et al., 2004). HDAC inhibitors enhance the acetylation of core proteins, which is linked to the formation of transcriptionally active chromatin in various cells. The expression of the LL-37/hCAP-18 gene was also reduced in some leukemia cells (Yang et al., 2003). In patients with acute myeloid leukemia, there was a marked reduction of LL-37/hCAP-18 expression in the peripheral blood compared with the level in healthy donors (An et al., 2005). In myeloid cells, cathelicidin gene is a direct target of the VDR and is strongly up-regulated by calcitriol (Gombart et al., 2005). The combination of TLR ligands (CpG oligodeoxynucleotides, CpG-ODN) LL-37 generated significantly better therapeutic tumor effects and enhanced survival in murine ovarian tumor-bearing mice compared with CpG-ODN or LL-37 alone (Chuang et al., 2009).

3. Role of vitamin D and its analog in cancer

3.1. The bacillus Calmette-Guerin (BCG) vaccination

The BCG vaccine was developed to provide protection against tuberculosis and has also been demonstrated to offer protection against cancer. The combination of BCG and ionizing radiation resulted in the induction of autophagy in colon cancer cells (Yuk et al., 2010). Intravesical BCG therapy has been demonstrated to reduce the recurrence rate and the risk of progression to muscle-invasive disease in patients with superficial bladder tumors (Herr et al., 1988). The BCG vaccination significantly prolongs the survival of patients with a malignant melanoma after initial surgical removed (Kölmel et al., 2005) and improved survival rates in patients with resected lung cancer (Repin, 1992). BCG inoculation delayed the tumor growth and prolonged the survival time in nude mice with leukemia (Wang et al., 2011c). BCG vaccination reduced the risk of lymphomas in a Danish population (Villumsen et al., 2009) and demonstrated to reduce the mortality, morbidity, and frequency of myeloic and chronic leukemia in children (Ambrosch et al., 1981). On the other hand, BCG-vaccinated infants are almost 6 times more likely to have sufficient vitamin D concentrations than unvaccinated infants 3 months after BCG vaccination, and this association remains strong even after adjusting for season, ethnic group and sex (Lalor et al., 2011). Among the vaccinated group, there was also a strong inverse correlation between the IFN-γ response to *M. tuberculosis* PPD and vitamin D concentration; infants with higher vitamin D concentrations had lower IFN-γ responses. Similarly, tuberculosis in cattle usually presents with a rapid transient increase in serum calcitriol within the first two weeks following infection (Rhodes et al., 2003). 1,25OHD-positive mononuclear cells were later identified in all of the tuberculous granulomas. During tuberculosis infection, alveolar macrophage-produced calcitriol plays a beneficial role by limiting inflammation-mediated tissue injury, potentiating NO production by stimulated monocytes/macrophages, inhibiting INF-γ production by stimulated $CD4^+$ cells, and suppressing the growth of *M. tuberculosis* (Ametaj et al., 1996; Rockett et al., 1998).

3.2. Matrix Metalloproteinase (MMPs)

MMPs are proteolytic enzymes responsible for extracellular matrix remodeling and the regulation of leukocyte migration through the extracellular matrix, which is an important step in inflammatory and infectious pathophysiology. MMPs are produced by many cell types including lymphocytes, granulocytes, astrocytes and activated macrophages. The MMP-1 expression is linked to sarcoma cell invasion (Garamszegi et al., 2011). MMP-2 expression is increased in gastric cancer cells (Partyka et al., 2012) and colorectal cancer (Dong et al., 2011). MMP-9 is expressed in many cancer cells, such as those associated with non-small-cell lung cancer (Peng et al., 2012), ovarian cancer invasion and metastasis (Zhang et al., 2011a), glioblastoma multiforme (Yan et al., 2011), and adamantinous craniopharyndioma (Xia et al., 2011). The MMP-2 and MMP-9 secreted by leukemic cells increase the permeability of blood brain barrier of the CNS by disrupting tight junction proteins (Feng et al., 2011b). In gastric cancer, MMP-2 and MMP-9 play an important role in tumor invasion and metastasis (Parsons et al., 1998). The risks for the development of hypophyseal adenoma and cervical neoplasia are greater in patients with MMP-1 polymorphisms (Altaş et al., 2010; Tee et al., 2012) than those with the wild-type allele. The MMP-2 polymorphism contributed to prostate cancer susceptibility in North India (Srivastava et al., 2012) and to the clinical outcome of Chinese patients with non-small cell lung cancer treated with first-line, platinum-based chemotherapy (Zhao et al., 2011). The MMP-7 polymorphisms are associated with esophageal squamous cell carcinoma and colorectal cancers (Manzoor et al., 2011; Dziki et al., 2011). The SPNs in the MMP-2 and MMP-9 region are associated with susceptibility to head and neck squamous cell carcinoma in an Indian population (Chaudhary et al., 2011). The SNPs of genes encoding MMPs (-1, -2, -3, -7, -8, -9, -12, -13, and -21) are related to breast cancer risk, progression, and survival (Wieczorek et al., 2012). Based on meta-analysis studies, the MMP-2 allele (-1306T) is a protective factor for digestive cancer risk (Zhang and Ren, 2011), the MMP-9 polymorphism is associated with a lower risk of colorectal cancer (Zhang et al., 2012a), and polymorphisms in the promoter regions of MMP-1, -3, -7, and -9 are associated with metastasis in some cancers (Liu et al., 2012). On the other hand, VDR-knock-out mice were shown to have an influx of inflammatory cells, phospho-acetylation of NF-κв, and up-regulated expression of MMP-2, MMP-9, and MMP-12 in the lung (Sundar et al., 2011). The *VDR TaqI* polymorphism is associated with decreased production of TIMP-1, a natural inhibitor of MMP-9 (Timms et al., 2002). In addition, calcitriol modulates tissue MMP expression under experimental conditions (Dean et al., 1996), down-regulates MMP-9 levels in keratinocytes, and may attenuate the deleterious effects of excessive TNF-α-induced proteolytic activity associated with cutaneous inflammation (Bahar-Shang et al., 2010). Calcitriol decreased the invasive properties of breast carcinoma cells and decreased MMP-9 levels in association with the increased levels of the tissue inhibitor of MMP-1 activity (Koli and Keshi-Oja, 2000). Calcitriol also inhibits endometrial cancer cell growth and is associated with decreased MMP-2 and MMP-9 expression

(Nguyen et al., 2011). Moreover, calciferol, calcitriol, and vitamin D analogs decreased MMP-2 and MMP-9 activities and inhibited prostate cancer cell invasion (Tokar and Webber, 2005; Schartz et al., 1997; Iglesias-Gato et al., 2011; Stio et al., 2011). A vitamin D analog has also been reported to reduce the expression of MMP-2, MMP-9, vascular endothelial growth factor (VEGF) and PTH-related peptide in Lewis lung carcinoma cells (Nakagawa et al., 2005). Taken together, these studies suggest that calcitriol may play an important role in the pathological processes in cancer by down-regulating the level of MMPs and regulating the level of TIMPs.

3.3. Wnt/β-catenin

The Wnt/β-catenin signaling pathway plays a pivotal role in the regulation of cell growth, cell development and the differentiation of normal stem cells. Wnt/β-catenin signaling is implicated in many human cancers, including gastrointestinal cancer, gastric cancer, colon cancer, melanoma, HCC, endometrial carcinoma, ovarian carcinoma, cervical cancer, papillary thyroid carcinoma, renal cell carcinoma, prostate cancer, parathyroid carcinoma, and hematological malignancies (White et al., 2012; Nuñez et al., 2011; Polakis, 2000; Li et al., 2012; Yoshioka et al., 2012; Guturi et al., 2012; Bulut et al., 2011; Gilber-Sirieix et al., 2011; Ueno et al., 2011; Svedlund et al., 2010; Ge and Wang, 2010). Calcitriol inhibits β-catenin transcriptional activity by promoting VDR binding to β-catenin and the induction of E-cadherin expression (Palmer et al., 2001). Paricalcitol, a vitamin D analog, suppressed β-catenin-mediated gene transcription and ameliorated proteinuria and kidney injury in adriamycin nephropathy (He et al., 2011). Most VDR variants fail to activate the vitamin D-responsive promoter and also fail to bind β-catenin or regulate its activity (Byers and Shah, 2007). VDR depletion enhances Wnt/β-catenin signaling and the tumor burden in colon cancer (Larriba et al., 2011). The action of cacitriol on colon carcinoma cells depends on the dual action of VDR as a transcription factor and a nongenomic activator of RhoA-ROCK and p38MAPK-MSK1, which are required for the inhibition of the Wnt/β-catenin signaling pathway and cell proliferation (Ordóñez-Morán et al., 2008). The *DICKKOFF*-4 gene induces a malignant phenotype, promotes tumor cell invasion, and angiogenesis in colon cancer cells and is repressed by calcitriol (Pendás-Franco et al., 2008a); whereas *DICKKOFF*-1 gene acts as a tumor suppressor in human colon cells and is up-regulated by calcitriol (Aguilera et al., 2007; Pendás-Franco et al., 2008b). The transcription factor TCF-4 acts as transcriptional repressor in breast and colorectal cancer cell growth. The TCF-4 and β-catenin binding partner are indirect targets of the VDR pathway. In the VDR knockout mouse, TCF-4 is decreased in the mammary gland when compared with a wild-type mouse. In addition, calcitriol increases TCF-4 RNA and protein levels in several human colorectal cancer cell lines (Beildeck et al., 2009). Furthermore, the Snail1 gene is associated with gastric cancer, melanoma, breast cancer, HCC, and colon carcinoma. Calcitriol inhibits the Wnt/β-catenin signaling pathway and is abrogated by Snail1 in human colon cancer cells (Larriba et al., 2007).

3.4. The Mitogen-Activated Protein Kinase (MAPK) pathways

The MAPK pathways provide a key link between the membrane bound receptors that receive these cues and changes in the pattern of gene expression, including the extracellular signal-regulated kinase (ERK) cascade, the stress activated protein kinases/c-jun N-terminal kinase

(SAPK/JNK) cascade, and the p38MAPK/RK/HOG cascade (Hipskind and Bilbe, 1998). In human colon cancer cells, calcitriol increases cytosolic Ca^{2+} concentration and transiently activates RhoA-ROCK, and then activates the p38MAPK-MSK signaling pathway (Ordóñez-Morán et al., 2008). In breast cancer cells, the MARK (JNK and p38) signaling pathway involved in calcitriol-induced breast cell death (Brosseau et al., 2010) and potentiated the cytotoxic action of calcitriol and TNF-α (Weitsman, et al., 2004). In murine squamous cell carcinoma cells, vitamin D induced apoptosis and selective induction of caspase-dependent MEK cleavage (McGuire et al., 2001). In an ovarian cancer animal model, vitamin D induced cell death and is mediated by the p38MAPK signaling pathway (Lange et al., 2010). In human promyeloblastic leukemia cells (HL60), vitamin D derivatives had anti-proliferative activity and activated MAPK signaling pathways (Ji et al., 2002). In human acute myeloid leukemia cells, calcitriol-induced differentiation is enhanced by the activation of MAPK signaling pathways (Zhang et al., 2011b).

3.5. The Prostaglandins (PGs)

Prostaglandins (PGs) play a role in inflammatory processes, and cyclooxygenase (COX) participates in the conversion of arachidonic acid in PGs. A variety studies have shown that prostaglandin signaling stimulates cancer cell growth and cancer progression. The regulation of PG metabolism and biological actions contribute to its anti-proliferation effects in prostate cells and calcitriol has been reported to regulate the expression of several key genes involved in the PG pathway, resulting in decreased PG synthesis (Moreno et al., 2005). The expression of the COX-2 gene is significantly increased in human gastric adenocarcinoma tissues compared with adjuvant normal gastric mucosal specimens (Ristimäki et al., 1997). There is inversely association between elevated COX-2 levels and decreased VDR expression in patients with breast and ovarian cancers compared with healthy women (Cordes et al., 2012). Calcitriol differentiated the human leukemic cell line (HL-60) and metabolized exogenous arachidonic acid to both COX products (predominantly thromboxane B_2 and PG E_2) and lipoxygenase products, including leukotriene B_4 (Stenson et al., 1988). In a mouse xenograft model of prostate cancer, the combination of cacitriol and dietary soy enhanced cacitriol activity in regulating target gene expression and increased the suppression of PG synthesis and signaling, such as COX-2, 15-hydroxyprostaglandin dehydrogenase (15-PGDH), and PG receptors. (Wang et al., 2012a). Calcitriol and its analogs have also been shown to selectively inhibit the activity of COX-2 (Aparna et al., 2008), and an inverse correlation exists between the expression of PG-metabolizing enzymes and reduced VDR expression in malignant breast cell lines (Thill et al., 2012). Taken together, these findings suggest that vitamin D may play a role in modulating the inflammatory process in cancer.

3.6. Oxidative stress

Reactive oxygen species (ROS) play a major role in various cell-signaling pathways. ROS activates various transcription factors and increases in the expression of proteins that control cellular transformation, tumor cell survival, tumor cell proliferation and invasion, angiogenesis, and metastasis. ROS has an important role in the initiation and progression of many cancers (Gupta et al., 2012; Marra et al., 2011; Zhang et al., 2011c; Wang et al., 2011c; Rogalska et al., 2011; Gupta-

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Elera et al., 2012). Single nucleotide polymorphisms of antioxidant defense genes may significantly modify the functional activity of the encoded proteins. Women with genetic variability in the iron-related oxidative stress pathways may be at increased risk of post-menopausal breast cancer (Hong et al., 2007). The *ala* variant of superoxide dismutase (SOD) is associated with a moderately increased risk of prostate cancer (Woodson et al., 2003). Based on meta-analysis studies, manganese SOD (MnSOD) polymorphisms may contribute to cancer development (Val-9Ala) (Wang et al., 2009b), prostate cancer susceptibility (Val-16Ala) (Mao et al., 2010), but not to breast cancer susceptibility (Val-16Ala) (Ma et al., 2010a). Calcitriol can also protect nonmalignant prostate cells from oxidative stress-induced cell death through the prevention of reactive oxygen species (ROS)-induced cellular injuries (Bao et al., 2008). Vitamin D metabolites and vitamin D analogs have been reported to induce lipoxygenase mRNA expression, lipoxygenase activity and ROS in a human bone cell line (Somjen et al., 2011). Vitamin D can also reduce the extent of lipid peroxidation and induce SOD activity in the hepatic anti-oxidant system of rats (Sardar et al., 1996). Moreover, the activation of macrophage 1α-hydroxylase results in an increase in 1,25OHD, which inhibits iNOS expression and reduces nitric oxide (NO) production by LPS-stimulated macrophages (Chang et al., 2004). This calcitriol production by macrophages may provide protection against the oxidative injuries caused by the NO burst. Calcitriol is known to inhibit LPS-induced immune activation in human endothelial cells (Equil et al., 2005), and calcitriol has also been shown to enhance intracellular glutathione pools and significantly reduce the nitrite production induced by the LPS (Garcion et al., 1999). Furthermore, overproduction of ROS induces DNA damage and leads to carcinogenesis. In the mouse colon, there was an inverse relationship between VDR levels and colonic hyperproliferation; the expression of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a maker of oxidative DNA damage, significantly increased with complete loss of VDR (Kállay et al., 2002). Vitamin D decrease 8-OHdG by 22% in the normal human colorectal mucosa (Fedirko et al., 2012). Calcitriol contributes to a reduction of the DNA intensify replication stress in lymphocytes (Halicka et al., 2012). In addition, vitamin D_3 up-regulated protein 1(VDUP1) is a regular for redox signaling and stress-mediated diseases (Chung et al., 2006). Taken together, these findings suggest that vitamin D modulates oxidative stress in cancer.

4. The use of vitamin D in cancer treatment

A number of clinical trials have used vitamin D_3 and calcitriol alone or in combination with anti-tumor agents. Most preclinical suggest that that the optimal anti-tumor effect of calcitriol and other analogs is seen with the administration of high dose calcitriol on intermittent schedule. A small number of single agent trials utilizing vitamin D_3 and calcitriol hace been conducted with limited success.

4.1. Vitamin D_3 trials

Fifteen patients were given 2,000 IU (50 microg) of cholecalciferol daily and monitored prospectively every 2-3 mo. There was a statistically significant decrease in the rate of PSA rise after administration of cholecalciferol compared with that before cholecalciferol. The median PSA doubling time increased from 14.3 months prior to commencing cholecalciferol to 25 months after commencing cholecalciferol. Fourteen of 15 patients had a prolongation of PSA doubling time after commencing cholecalciferol (Woo et al., 2005). Breast cancer patients with bone metastases received 10,000 IU of vitamin D_3 daily for 4 months. There was a significant reduction in the number of sites of pain (Amir et al., 2010). Arlet al. (2012) reported on an unexpected observation of a spectacular 13-month remission of chronic lymphocytic leukemia after the administration of cholecalciferol in an elderly patient. Dietary vitamin D_3 and calcitriol have been shown to demonstrate equivalent anticancer activity in mouse xenograft models of breast and prostate cancers (Swani et al., 2012).

4.2. Calcitriol trials — Single agent

In a clinical trial, high-dose calcitriol decreased prostatic-specific antigen (PSA) levels by 50% and reduced thrombosis in prostate cancer patients (Beer et al., 2003 & 2006). In hepatocellular carcinoma, calcitriol and its analogs have been reported to reduce tumor volume, increase hepatocarcinoma cell apoptosis by 21.4%, and transient stabilize serum alpha-fetoprotein levels (Dalhoff et al., 2003; Luo et al., 2004; Morris et al., 2002). The vitamin D analog, 19-Nor-2α-(3-hydroxypropyl)-1α,25-dihydroxyvitamin D_3, is a potent cell growth regulator with enhanced chemotherapeutic potency in liver cancer cells (Chiang et al., 2011). Alphacalcidol, a vitamin D analogue, has been demonstrated significant antitumor activity in patients with low-grade non-Hodgkin's lymphoma of the follicular, small-cleaved cell type (Raina et al., 1991). In patient with parathyroid cancer, vitamin D has been shown to prevent or delay the progression of recurrence (Palmieri-Sevier et al., 1993). Treatment with paricalcitol inhibited gastric cancer cell growth and peritoneal metastatic gastric cancer volume was significantly lower in paricalcitol treated mice (Park et al., 2012). Calcitriol treatment of breast cancer cell lines led to significantly fewer inflammatory breast cancer experimental metastases as compared to control (Hillyer et al., 2012).

4.3. Calcitriol trials — In combination

Calcitriol additively or synergistically potentiates the antitumor of other types of chemotherapeutic agents. Calcitriol enhances cellular sensitivity of human colon cancer cells to 5-fluorouracil (Liu et al., 2010). Combination of calcitriol and cytarabine prolonged remission in elderly patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) (Slapak et al., 1992; Ferrero, et al., 2004). A renal cell carcinoma patient with multiple bone metastases that were almost completely resolved after treatment with vitamin D and interferon-α (Fujioka et al., 1988). In a prospective study, a combination of active vitamin D and α- interferon has shown to be effective in patients with metastatic renal cell carcinoma (Obara et al., 2008). Calcitriol promotes the anti-proliferative effects of gemcitabine and cisplatin in human bladder cancer models (Ma et al., 2010b), and also potentiates antitumor activity of paclitaxel and docetaxel (Hershberger et al., 2001; Ting et al. 2007). A phase II study showed that high-dose calcitriol with docetaxel may increase time to progression in patients with incurable pancreatic cancer when compared with docetaxel monotherapy (Blanke, 2009).Vitamin D_3 treatment significantly suppressed the viability of gastric cancer and cholangiocarcinoma cells and also had a synergistic effect with other anti-cancer drugs, such as paclitaxel, adriamycin, and vinblastine (Baek et al., 2011). In locally advanced or cutaneous metastatic breast cancer, topical calcipotriol treatment reduced the diameter of treated lesions that contained vitamin D receptor (*VDR*) (Bower et al., 1991). Calcitriol potentiates both carboplatin and cisplatin-mediated growth inhibition in breast and prostate cancer cell lines (Cho et al., 1991; Moffatt et al., 1999). Tamoxifen and calcitriol or its analog used together to enhance growth inhibition in breast cancer cells than either agent alone (Vink-van Wijngaarden et al., 1994). Cacitriol sensitizes breast cancer cells to doxorubicin through the inhibition of the expression and activity of cytoplasmic antioxidant enzyme (Ravid et al., 1999). Calcitriol may increase cisplatin sensitivity in chemotherapy-resistant testicular germ cell cancer-derived cell lines (Jørgensen et al., 2012). Combination of retinoic acid and vitamin D analog exert synergistic growth inhibition and apoptosis induction on hepatocellular cancers cells (Zhang et al., 2012b). The combination of calcitriol and dietary soy resulted in substantially greater inhibition of tumor growth than the inhibition achieved with either agent alone in a mouse xenograft model of prostate cancer (Wang et al., 2012a).

5. Conclusion

Vitamin D has a role in the prevention and treatment of cancer. Genetic studies have provided the opportunity to determine what proteins link vitamin D to the pathology of cancer. Vitamin D also exerts its effect on cancer via non-genomic mechanisms. As a result, it is imperative that vitamin D levels in patients with cancer be followed. Many studies use the relationship between serum PTH and 25OHD to define the normal range of serum 25OHD. According to the report on Dietary Reference Intakes for vitamin D and calcium by the Institute of Medicine (IOM), persons are at risk of deficiency at serum 25OHD levels less than 30 nmol/L. Saliba et al. (2011) suggested that a 25OHD threshold of 50 nmol/L is sufficient for PTH suppression and prevention of secondary hyperparathyroidism in persons with normal renal function. It is necessary to check serum $25OHD_3$ and parathyroid hormone (PTH) status in cancer patients. Serum levels of PTH have been reported to correlate with PSA levels and colorectal cancer (Skinner & Schwartz, 2009; Charalampopoulos et al., 2010). Some authors proposed that, in patients with normal calcium levels, the serum $25OHD_3$ levels should be stored to > 55ng/ml in cancer patients (colon, breast, and ovary) (Garland et al., 2007). Calcitriol, $1{,}25OHD_3$, is best used for cancer treatment, because of its active form of vitamin D_3 metabolite, suppression of PTH levels (acted as cellular growth factor), and their receptors presented in most of human cells. However, monitor of serum $25OHD_3$ after taking calcitriol is not necessary because calcitriol inhibits the production of serum $25OHD_3$ by the liver (Bell et al., 1984; Luong & Nguyen, 1996). The main limitation to the clinical widespread evolution of $1{,}25OHD_3$ is its hypercalcemic side-effects.

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