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DNA Repair in Despair—Vitamin D Is Not Fair

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ABSTRACT

The role of vitamin D as a treatment option for neoplastic diseases, once considered to have a bright future, remains controversial. The preclinical studies discussed herein show compelling evidence that Vitamin D Derivatives (VDDs) can convert some cancer and leukemia cells to a benign phenotype, by differentiation/maturation, cell cycle arrest, or induction of apoptosis. Furthermore, there is considerable, though still evolving, knowledge of the molecular mechanisms underlying these changes. However, the attempts to clearly document that the treatment outcomes of human neoplastic diseases can be positively influenced by VDDs have been, so far, disappointing. The clinical trials to date of VDDs, alone or combined with other agents, have not shown consistent results. It is our contention, shared by others, that there were limitations in the design or execution of these trials which have not yet been fully addressed. Based on the connection between upregulation of JNK by VDDs and DNA repair, we propose a new avenue of attack on cancer cells by increasing the toxicity of the current, only partially effective, cancer chemotherapeutic drugs by combining them with VDDs. This can impair DNA repair and thus kill the malignant cells, warranting a comprehensive study of this novel concept. J. Cell. Biochem. 117: 1733–1744, 2016.

KEY WORDS: VITAMIN D; CALCITRIOL; VITAMIN D DERIVATIVES; DIFFERENTIATION; APOPTOSIS; CELL CYCLE

Two developments in the 1980s generated major excitement in the cancer research and treatment community. First, Breitman et al. [1981] reported that human myeloid leukemia cells in established culture (HL60 and U937 cells), as well as acute promyelocytic leukemia (APL) cells in primary culture differentiated into granulocytes in response to exposure to retinoic acid. Following the production of All Trans Retinoic Acid (ATRA) in Shanghai and first treatment of patients with APL there [Huang et al., 1988], subsequent studies established that ATRA induces complete clinical remissions of the disease. Incorporation of ATRA into APL therapy is now acknowledged to be superior to the previously conventional cytotoxic anthracycline therapy, through in vivo terminal differentiation of APL blasts to granulocytes [Castaigne et al., 1990].

In the same time frame, several observations indicated that the physiological form of vitamin D, 1,25-dihydroxyvitamin D_3 (calcitriol), can induce differentiation of neoplastic cells and terminate their proliferation. Abe et al. [1981] and Tanaka et al. [1983] reported that calcitriol induces both mouse and human acute myeloid leukemia (AML) cells to differentiate to monocyte lineage, but not to granulocytes. Also, Colston et al. [1981] demonstrated growth inhibition of calcitriol-treated malignant melanoma cells. Numerous other studies then further supported the notion that vitamin D-based

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ATM, ataxia-telangiectasia mutated kinase; ATR, Rad3-related kinase; ATRA, all trans retinoic acid; CDKIs, cyclin-dependent kinases inhibitors; Chk2, checkpoint 2 kinase; DD, death domain; DDR, DNA damage response; GPCRs, G-protein coupled receptors; IGFR, insulin-like growth factor receptor; KSR, kinase suppresor of Ras; MAPKS, mitogen activated kinases; MDC1, DNA checkpoint protein 1; PI3 K, phosphatidylinositol-3 kinase; PIDD, p53-inducible protein with a death domain; PKC, protein kinase C; Rb, retinoblastoma protein; RIP1, receptor-interacting protein kinase 1; RPA, replication protein A; RXRα, retinoid X receptor alpha; TCF4, T-cell factor 4; TNFα, tumor necrosis factor alpha; VDDs, vitamin D derivatives; VDR, vitamin D receptor; VDRE, vitamin D response elements.

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differentiation therapy can be a therapeutic modality for human leukemia and solid tumors [Studzinski et al., 1985].

The initial enthusiasm for vitamin D as candidate for differentiation therapy in the clinic was soon tempered by the realization that the concentrations of vitamin D required to induce differentiation or growth arrest of malignant human cells cannot be achieved in the clinic since these would be incompatible with life. Undeterred, this has stimulated the field of differentiation therapy to search for synthetic analogs of vitamin D (VDDs) which would be less calcemic, yet retain differentiation-inducing properties [Jones et al., 1998]. Several thousands of such VDDs have been synthesized, and the search for an ideal VDDs is still continuing [Trynda et al., 2015; Teske et al., 2016], but as detailed below, there have been no outstanding successes in this area. However, this effort has not been entirely a waste of resources, as some analogs have found place in the treatment regimens of non-neoplastic diseases, for example, psoriasis and kidney dialysis patients [Brown, 2007].

Now, three decades after demonstration of the possibility of differentiation therapy, VDDs are still seeking vindication in cancer therapy. But even with retinoid based therapy, there is a realization that although ATRA is able to induce complete remission in almost all patients with APL, it cannot eliminate the leukemic clone. To be most effective, ATRA must be used in combination with arsenic trioxide-based chemotherapy [Burnett et al., 2015]. It is, therefore, likely that any success with VDDs in treatment or cure of human cancers will require combination with other compounds. Some possibilities are discussed in the following sections of this article.

IN VITRO STUDIES OF VDDs-INDUCED DIFFERENTIATION OF NEOPLASTIC CELLS, THE ASSOCIATED CELL CYCLE ARREST, OR APOPTOSIS

CALCITRIOL-INDUCED DIFFERENTIATION

Calcitriol is the physiologically active form of vitamin D that belongs to the family of secosteroid hormones. Its primary action is the regulation of intracellular calcium and phosphorus absorption [Dusso et al., 2005; Morris, 2014; Christakos et al., 2016]. Moreover, calcitriol exhibits pleiotropic functions by regulating the innate and adaptive immune responses, or growth and differentiation of multiple normal and cancer cells [Sarkar et al., 2016]. The main mechanism by with calcitriol exerts its cellular activity is transcriptional activation [Marcinkowska, 2001b; Gocek et al., 2007, 2008]. Within the cell, calcitriol binds to the Vitamin D Receptor (VDR), which belongs to the superfamily of nuclear receptors that are ligand-activated transcription factors [Dusso et al., 2005]. After ligation, VDR as a homodimer or a heterodimer with Retinoid X Receptor alpha (RXRα), translocates from the cytosol to the cell nucleus. The dimeric complex then binds to the Vitamin D Response Elements (VDRE) located in the promoter regions of the target genes [Carlberg et al., 1993]. Around 3000 calcitriol-regulated target genes have been identified by the Chip-seq technique [Ramagopalan et al., 2010; Heikkinen et al., 2011]. These include genes essential for cell cycle regulation and differentiation, such as Kinase Suppressor of Ras (KSR), $p27^{Kip1}$, CD14, β-catenin, E-cadherin [Sheng et al., 2015]. Some of the differentiation-related signaling pathways studied in several cell systems involve Mitogen Activated Kinases (MAPKs) [Tong et al., 1999; Wang et al., 2000; Wang and Studzinski, 2001b; Qi et al., 2002], Phosphatidylinositol-3 Kinases (PI3Ks)-AKT [Marcinkowska et al., 1998; Zhang et al., 2006], KSR [Studzinski et al., 2005], ERK5-C/EBPβ-MEF2C [Wang et al., 2006; Zheng et al., 2015], and protein kinase C (PKC) [Marcinkowska et al., 1997]. The summaries of the calcitriol-induced signaling of the regulation of cell proliferation and survival principally applicable to solid tumors (Fig. 7 in reference [Christakos et al., 2016]) and AML cells (Figs. 3 and 4 in reference [Gocek and Studzinski, 2015] have recently been published, and can supplement our narrative below.

The principal MAPKs signaling cascades which are activated by calcitriol during differentiation include ERK1/2, ERK5, JNKs, and p38 [Wang and Studzinski, 2001a, 2006; Raman et al., 2007; Ordonez-Moran et al., 2008; Gocek and Studzinski, 2015]. These kinases constitute the downstream part of a signaling machinery initiated by growth factors, cytokines or stresses through the small GTPase Ras, then protein kinases such as Raf1, Cot1, MTK/DLK or ASK1/TAK1/PTK1, and MAP2Ks (MEK1/2, MEK5, MKK7/MEK4 or MEK3/6) which phosphorylate ERK1/2 and ERK5 [Wang et al., 2014, 2015b]. Finally, MAPKs activate various transcription factors, such as c-Myc, c-Jun, c-Fos or Sp1, which in turn activate genes responsible for differentiation, proliferation or cell survival [Chambard et al., 2007; Rasola et al., 2010; Maurer et al., 2011; Deschenes-Simard et al., 2014].

PI3Ks-AKT pathway can be driven by G-protein Coupled Receptors (GPCRs), tyrosine kinases (receptor and non-receptor) or Ras downstream to the production of the lipid second messenger, phosphatidylinositol (3,4,5) triphosphate (PIP_3) from phosphatidylinositol (4,5) bisphosphate (PIP_2). AKT specifically binds the 3′-phosphorylated inositol lipids throughout plekstrin homology domain, hence PIP_3 recruits AKT to the cell membrane. Phosphorylated AKT initiates downstream signaling, such as mTOR activation or FOXO inhibition leading to the regulation of differentiation and/or cell cycle block [Ciruelos Gil, 2013; Jabbour et al., 2014]. AKT also can phosphorylate the pro-apoptotic protein Bad, which leads to its degradation, thus being a major factor in increasing the survival of a large variety of human cells [Datta et al., 1997; Zhang et al., 2006; Xu et al., 2016]. Activation by calcitriol of signaling pathways mentioned above is cell-type and cell-context specific, although the pathways may overlap in several types of the cells. An important consideration is the variable influence of calcitriol on cells from different tissue types. For instance, in breast, colon, ovarian, pancreatic, and prostate cancer cells, calcitriol induces inhibition of proliferation or apoptosis, while in myeloid cells, calcitriol increases cell survival or may trigger autophagy.

DIFFERENTIATION-ASSOCIATED CELL CYCLE ARREST

Calcitriol and its analogs inhibit proliferation of diverse normal and cancer cells by arresting them in the G1/S phase of the cell cycle [Wang et al., 1998] or inhibiting the G2 to M transition [Godyn et al., 1994]. Induction of cell cycle arrest occurs by calcitriol-induced upregulation of Cyclin-Dependent Kinases inhibitors (CDKIs) such as $p27^{Kip1}$ and $p21^{Cip1}$ [Steinman et al., 1994; Wang et al., 1996]. Functional VDRE has been identified in the promoter region of $p21^{Cip1}$ and thus it can be directly regulated by calcitriol [Liu et al.,

1996]. Unlike $p21^{Cip1}$, $p27^{Kip1}$ has no VDRE and its regulation by calcitriol is far more complicated. It occurs either transcriptionally or post-transcriptionally. One of the reported mechanisms of transcriptional activation of $p27^{Kip1}$ involves physical interaction between VDR and Specificity Protein 1 (Sp1) [Inoue et al., 1999; Huang et al., 2004]. Post-transcriptionally, its expression may be inhibited, for instance, by microRNA-181a in AML cells [Cuesta et al., 2009; Wang et al., 2009]. The exposure of AML cells to calcitriol reduces the level of microRNA-181a, and thus increases the level of $p27^{Kip1}$ and the cell cycle block. However, the principal mechanism of the regulation of cellular abundance of $p27^{Kip1}$ may be its degradation by the ubiquitin-proteosome pathway, regulated by the E3 ligase SCF-Skp2 and accessory proteins [Pagano et al., 1995; Wu et al., 2012]. Interestingly, upregulation of CDKIs by calcitriol is associated with calcitriol-induced increased expression of Retinoblastoma protein (pRb) and its later phosphorylation [Ji et al., 2002; Washington et al., 2011]. This leads to the binding of pRb to E2F transcription factor causing inactivation of E2F target proteins, such as cyclin E and c-Myc, and subsequent cell cycle block [Brelvi and Studzinski, 1986; Gartel et al., 2001; Wilson et al., 2002].

In colon cancer cells, calcitriol enhances the expression of E-cadherin and subsequent transport of β-catenin from the cell nuclei to plasma membrane. In proliferating cells β-catenin interacts with T-cell Factor 4 (TCF4) [Palmer et al., 2001; Larriba et al., 2013]. This interaction is controlled by Wnt and its surface receptor Frizzled. Binding of β-catenin to VDR takes place by the AF2 domain of VDR [Shah et al., 2006] and leads to the loss of β-catenin from the transcriptional complex with TCF4. As a consequence, the expression of TCF4 target genes (c-Myc and cyclin D1) becomes impaired and cell cycle progression becomes inhibited [Larriba et al., 2013].

The sequence of events initiated by calcitriol described above, leading to differentiation and associated with proliferation blockage, seems to occur in many normal and cancer cells. These include keratinocytes, hematopoietic, prostate, breast, pancreatic, colon, hepatoma, osteosarcoma, squamous, thyroid, ovarian, and neuroblastoma cells. Of note, inhibition of cell proliferation by calcitriol is not always related to cell differentiation. Examples are smooth muscle cells [Damera et al., 2009], or pituitary corticotroph cells [Liu et al., 2002].

The anti-proliferative effects of calcitriol can also be due to activation of genes and proteins responsible for apoptosis of cancer cells as described below in Section entitled "VDDs Can Decrease Cell Survival".

EXAMPLES OF VDDs INCREASING OR DECREASING CELL SURVIVAL

VDDs CAN INCREASE CELL SURVIVAL

In some cells, such as fibroblasts, keratinocytes, AML and primary melanoma, calcitriol-induced differentiation is accompanied by increased cell survival and decreased apoptosis [Sauer et al., 2005; Zhang et al., 2006].

Calcitriol-induced differentiation of AML cells can be divided into several phases. During the initial phase, the cells proliferate normally and cell cycle progression is driven by the high levels of MEK1/2, ERK1/2, JNKs [Marcinkowska, 2001a; Wang et al., 2003]. In a latter phase, Raf1 protein activates ribosomal S6 kinase $p90^{RSK}$ that together with other kinases, such as ERK1/2 and ERK5, activates the master transcription factor for monocytes/macrophages differentiation, C/EBPβ [Marcinkowska et al., 2006; Wang et al., 2014]. Pro-survival signals transmitted from Raf1 to downstream targets are augmented by KSR1 and KSR2, essential for Raf1 activation and/or phosphorylation [Wang et al., 2007]. KSR2 knockdown decreases cell survival, which is accompanied by reduced Bcl2/Bax and Bcl2/Bad ratios and increased cleavage of caspase 3 [Wang et al., 2008]. Moreover, during the later phase of calcitriol-induced differentiation of AML cells, elevated expression of other anti-apoptotic proteins, Bcl-xl and Mcl1 facilitates differentiation by increasing cell survival [Xu et al., 1993; Wang and Studzinski, 1997]. Additionally, in calcitriol-induced differentiating AML cells expression of pro-apoptotic protein Bim is inhibited by microRNA-32 [Gocek et al., 2011].

Cytoprotective effect of calcitriol was also found in fibroblasts, keratinocytes and primary melanocytes [Sauer et al., 2003, 2005]. In these cells, sphingosine 1-phosphate was identified as a downstream mediator of calcitriol actions. In fibroblasts and keratinocytes, enhanced intracellular Bcl-2/Bax ratio was identified as a major cause of protection against apoptosis [Sauer et al., 2005].

VDDs CAN DECREASE CELL SURVIVAL

Calcitriol can also activate genes and proteins responsible for apoptosis of cancer cells, such as breast, colon, and prostate [Welsh et al., 1995; Aggarwal et al., 2016]. It was shown that calcitriol activates the pro-apoptotic proteins Bak and Bax and suppresses the anti-apoptotic Bcl family members (Bcl2 and Bcl-xl) [Wagner et al., 2003; Kizildag et al., 2010]. This suppression causes the influx of cytochrome c from the mitochondria to the cytoplasm and triggers the activation of the downstream caspase 3 as well as the upstream initiator protease caspase 9, and the induction of apoptosis [Guzey et al., 2002; Suares et al., 2015]. The mechanism of calcitriol-induced apoptosis varies with the cell type and can be mediated by either p53-dependent, or independent pathways.

Moreover, it has been shown that calcitriol may induce apoptosis by dysregulation of the signaling pathways activated by different growth factors and its receptors. It down-regulates Insulin-like Growth Factor Receptor (IGFR) [Maestro et al., 2003] as well as up-regulates Tumor Necrosis Factor alpha (TNFα) [Golovko et al., 2005].

It was also shown that either calcitriol or its analogs, EB1089 and ILX23-7553 can potentiate the response to ionizing irradiation [Sundaram et al., 2000; Demasters et al., 2006]. For analog EB1089, such activity was detected in MCF-7 breast tumor xenografts in nude mice [Sundaram et al., 2003]. The effect of EB1089 on the radiation response did not interfere with DNA repair. It seems that cell death induced by irradiation followed by EB1089 treatment is a consequence of alterations in signaling pathways downstream of the DNA damage. These signaling pathways may also involve the generation of reactive oxygen species, acceleration of cell senescence and c-Myc independent apoptosis, as well as p53-dependent cell death by autophagy [Demasters et al., 2006].

Moreover, calcitriol may trigger an "autophagic switch" and reprogram ZR-75-1 breast cancer cells from cytoprotective autophagy with radiation alone, to a cytotoxic autophagy with

the combinatorial treatment [Wilson et al., 2011; Bristol et al., 2012]. Although interesting, it should be noted that the analogs used in these studies are no longer available from the manufacturers.

CLINICAL EXPERIENCE WITH VDDs IN NEOPLASTIC DISEASES

Poor responsiveness to standard chemotherapy is still a problem for a significant number of patients with neoplastic diseases. Although the current focus in the field is on individualized therapy based on molecular features of the disease, the great heterogeneity of mutations in most cancer cells makes this a remote aim. Thus, the possibility that a differentiation-based approach can be used for a large subset of cancer patients has been attractive. However, the attempts to utilize the differentiation properties of VDDs have had so far minimal success, possibly due, at least in part, to the variable levels of vitamin D receptors in the malignant cells and problems of designing appropriate conditions for clinical trials [Trump et al., 2010; Krishnan et al., 2012; Marchwicka et al., 2014].

The principal attempts to demonstrate the therapeutic utility of VDDs were directed to prostate, breast, and colorectal cancers, as well as AML cells. Although VDDs have a clear effect on differentiation of AML cells, described above, it could have been expected that VDDs may have an easily detected effect on this disease. However, as summarized in a review by Kim et al. [2012] which lists clinical trials mainly conducted in the early 1990s, administration of VDDs in these trials have not led to any major advances in the treatment of AML. Additionally, Harrison and Bershadskiy [2012] described these clinical trials in depth and listed two more trials in patients with MDS, often a pre-leukemic disease. However, neither trial led to dramatic or promising results. More recently, several other trials of VDDs have been conducted in MDS patients; but the results of those have not yet appeared in the literature, and the only phase III trial that could be found at this time (NCT00804050) has been terminated. Thus, although it is unclear whether VDDs, with or without potentiators that were used in the majority of experiments reported to date, will have a significant therapeutic effect in AML, it has been recently noted that low circulating 25(OH) vitamin D_3 levels are associated with adverse outcome in intensively treated adult AML [Lee et al., 2014].

The results of the effects of VDDs on solid tumors are also not definitive yet, similarly to other diseases, such as secondary hyperparathyroidism or rheumatoid arthritis. Several recent trials of calcitriol, mostly in combination with other compounds, have been closed without clear results [Ramnath et al., 2013] (Table I), but a larger number are continuing (Table II).

In the earlier reported trials, the effects of calcitriol on prostate cancer varied from encouraging [Liu et al., 2003; Wagner et al., 2013; Medioni et al., 2014] to no significant association between serum vitamin D and survival [Gupta et al., 2015], although it was remarked by others that vitamin D may have different effects for different stages of prostate cancers [Schenk et al., 2014]. In breast cancer, a recent I-SPY trial reported that pretreatment vitamin D levels had no impact on tumor response to neoadjuvant chemotherapy in women with breast cancer [Clark et al., 2014]. Also, an NIH sponsored trial of daily supplementation with vitamin D_3 (1000 IU), calcium (1200 mg), or both after removal of colorectal adenomas did not significantly reduce the risk of recurrent colorectal adenomas over a period of 3–5 years [Baron et al., 2015]. However, the authors of that report made several caveats, including the point that the dose of vitamin D may not have been sufficient, a not unlikely reason for a lack of effect. A bright spot in this survey is the report that circulating levels of vitamin D may be an important determinant of the development of follicular lymphoma as it was found that low serum vitamin D levels were associated with inferior survival of patients with this disease [Kelly et al., 2015].

As mentioned above, problems in drawing conclusions regarding the efficacy of VDDs in neoplastic diseases based on the clinical trials reported to date include the great heterogeneity of the patient populations studied, and the variability in the dose, schedule, and the chemical nature of the VDDs used. Thus, as of this date clinical trials of VDDs have not changed any treatment paradigms, and chemotherapy and irradiation are still the most commonly used in anti-cancer treatment. Thus, a better understanding of the signaling pathways underlying VDDs actions may be essential for future advances in the field. One possibility is that VDDs interfere with DNA repair in certain situations and this can be exploited the cancer therapy.

DNA DAMAGE, DNA DAMAGE RESPONSE (DDR), AND DNA REPAIR

Many chemotherapeutic agents useful for treatment of neoplastic diseases induce DNA damage, and since VDDs may augment their effects [Wang et al., 2015a], it is important to be able to analyze the mechanisms involved. Although there are multiple ways that cancer chemotherapeutic agents can damage DNA, the principal ones include alkylating agents such as nitrogen mustards or mitomycin C which form DNA crosslinks [Volpato and Phillips, 2007; Carreras

TABLE I. Selected Completed/Terminated Clinical Trials With Calcitriol During the Years 2009–2015

Study number	Type of cancer	Compounds	Phase	Comments/completion year
NCT00794547	Non-small-cell lung carcinoma	Calcitriol, cisplatin, docetaxel	I/II	Pharmacokinetics studies; results published/2013 [Ramnath et al., 2013]
NCT00524589	Androgen independent prostate cancer	Calcitriol, dexamethasone	II	Interventional studies; closed due to absence of results/2014
NCT01093092	Inoperable advanced solid tumors	Calcitriol, cisplatin, gemcitabine hydrochloride	I	Pharmacological studies;terminated due to absence of results/2015
NCT01293682	Breast cancer	Calcitriol	II	Efficacy and feasibility studies; closed due to absence of results/2015

TABLE II. Selected Ongoing Cancer-Related Clinical Trials With Calcitriol During the Years 2009–2015

Study number/start date	Main goal of study	Type of cancer	Type of study	Intervention	Phase
NCT02172651/07.2014	Identification of transcriptional targets of calcitriol	Colon (stage II and III)	Interventional; pharmacokinetics/ dynamics studies	Drug: Calcitriol 10,000 IU, 1× daily	0
NCT01516216/03.2012	Effects of calcitriol supplementation	Colon (metastatic, untreated)	Interventional; efficacy studies	Drug: FOLFOX + bevacizumab Suppl: Calcitriol 400 IU, 1× daily	II
NCT01150877/06.2010	Therapeutic effect and the safety of high-dose calcitriol supplementation	Colon (stage IV)	Interventional; safety/ efficacy studies	Drug: Cacitriol raising serum 25-hydroxy-vitamin D conc. to 200–250 nmol	I/II
NCT01965522/10.2013 NCT02288806/11.2014	Anti-proliferative effects of calcitriol and melatonin	Breast (early stage)	Interventional; efficacy studies	Drug: Calcitriol 2000 IU/day Drug: Melatonin: 20 mg/day	II
NCT02603757/11.2015	Effectiveness of calcitriol supplementation for patients requiring adjuvant chemotherapy	Colon (stage III)	Interventional; efficacy studies	Drug: Calcitriol 2000 IU/day	Pilot study
NCT01631526/06.2012	To validate a short-term calcitriol loading and maintenance dose	Lung (advanced)	Interventional; pharmacokinetics/ dynamics studies	Drug: Calcitriol: 50,000 IU, weekly Drug: Calcitriol 20,000 IU/day for 14 days followed by 10,000 IU/ day for 7 days	II
NCT01759771/12.2012	To compare the expression of molecular biomarkers, prognostically relevant to prostate cancer progression	Prostate (early stage)	Interventional; safety/ efficacy studies	Drug: Calcitriol 4000 IU 1× daily	II
NCT01988090/11.2013	Controlled trial of high dose vs. standard dose of calcitriol after aromatase inhibitors treatment	Breast	Interventional; safety/ efficacy studies	Drug: Calcitriol 800 IU	II
NCT02066688/02.2014	A randomized controlled trial in prevention	Colon	Interventional; safety/ efficacy studies	Drug: Calcitriol 50,000 IU Drug: Folic acid 1 mg 1×daily Drug: Folic acid + Calcium (1200 mg daily) + Calcitriol (250 IU daily) Drug: calcium 1200 mg daily	II/III
NCT02186015/07.2014	Safety, feasibility and efficacy of supplementation	Breast (metastatic)	Interventional; safety studies	Drug: Cholecalciferol 50,000 IU weekly for 8 weeks	I
NCT01608451/05.2012	Effect of cholecalciferol as an antiproliferative, cytotoxic and apoptotic agent	Breast (large, operable)	Interventional; safety/ efficacy studies	Drug: Cholecalciferol 300,000 IU/ml	III
NCT02532062/08.2015	Cholecalciferol influence on pulmonary function, on promoters methylation, proteins expression	Lung	Interventional; safety/ efficacy studies	Drug: Progesterone 500 mg Drug: Cholecalciferol 4000 IU/day for a year Drug: Multivitamin (incl 4000 IU/ day of cholecalciferol for a year	II
NCT01425476/04.2011	Cholecalciferol and celecoxib synergistic effect on prostaglandins metabolism and tumor size	Breast	Interventional; pharmacodinamics studies	Drug: Cholecalciferol 400 or 2000 IU daily for 30 days Drug: Celecoxib 400 mg	I/II
NCT01787409/06.2013	Cholecalciferol influence on improving survival in patients with newly diagnosed blood cancers	Lymphomas and leukemias	Interventional; safety/ efficacy studies	Drug: Cholecalciferol	N/A
NCT01820299/03.2013	The role of plant-derived phytochemicals and cholecalciferol in reduction of systemic inflammation	Solid cancers (gastrointestinal, lung, breast, prostate, lymphoma or cancer of the lymph nodes)	Interventional; safety/ efficacy studies	Drug: Cholecalciferol 4000 IU daily	I
NCT02064946/02.2014	Efficacy of a high dose cholecalciferol supplementation	Prostate	Interventional; efficacy studies	Drug: Grape seed extract Drug: Cholecalciferol 50,000 IU along with daily multivitamin	II

(*Continued*)

TABLE II. (*Continued*)

Study number/start date	Main goal of study	Type of cancer	Type of study	Intervention	Phase
	in reducing androgen deprivation therapy			(600 IU cholecalciferol + calcium 210 mg/day) and calcium (1000 mg/day) for 24 weeks	
NCT02304757/11.2014	The effects of 99Tc-MDP, calcium containing cholecalciferol alone and fosamax in postmenopausal women with DTC and decreased bone mineral density	Thyroid (differentiated)	Interventional; efficacy studies	Drug: 99Tc-MDP99Tc-MDP	N/A
NCT01769625/01.2013	Changes in protein and gene methylation related to the breast cancer	Breast	Interventional; safety/ efficacy studies	Drug: Caltrate (Calcium 600 mg and cholecalciferol 125 IU) Drug: Cholecalciferol 400 IU or 2000 IU daily for 30 days	I/II
NCT02461979/05.2015	The role of VDR gene polymorphisms in hepatocarcinogenesis	Liver	Interventional	Drug: Celecoxib 400 mg Drug: Cholecalciferol	N/A
NCT00887432/04.2009	The influence of cholecalciferol on treating patients with localized prostate cancer	Prostate	Interventional; efficacy studies	Drug: Cholecalciferol	II/III
NCT02100423/03.2014	The efficacy (activity) and tolerability studies of curcumin and cholecalciferol combination	Chronic lymphocytic leukemia (stage 0–II), small lymphocytic lymphoma	Interventional; efficacy studies	Drug: Cholecalciferol Drug: Curcumin	II
NCT02274623/10.2014	The effect of CTAP101 on serum calcium, plasma intact parathyroid hormone and vitamin D metabolites	Breast, prostate, bone neoplasms, hypocalcemia, secondary hyperparathyroidism	Interventional; safety studies	Drug: Calcifediol (CTAP101) 30 μg daily for 4 weeks	I
NCT02030860/01.2014	Pilot, pharmacodynamic, genomic studies of neoadjuvant Paricalcitol to target the microenvironment in resectable pancreatic cancer	Adenocarcinoma of the pancreas	Interventional; safety/ efficacy studies	Drug: Paricalcitol 25 μg 3×/weekly Drug: Abraxane 125 mg/m^2 1× for 3 days Drug: Gemcitabine 1000 mg/m^2 1× for 3 days	Pilot studies
NCT02336087/01.2015	Feasibility of the combination of gemcitabine hydrochloride, paclitaxel albumin-stabilized nanoparticle formulation, metformin hydrochloride, and a dietary supplement	Adenocarcinoma of the pancreas (stage IV)	Interventional; safety studies	Drug: Gemcitabine Hydrochloride Drug: Paclitaxel Albumin-Stabilized Nanoparticle Formulation Drug: Metformin Hydrochloride	I
NCT02553447/09.2015	The influence of cholecalciferol on survival rate in patients	Chronic lymphocytic leukemia, non-Hodgkin lymphoma	Interventional; efficacy studies	Drug: Cholecalciferol	II
NCT01518959/01.2012	The role of cholecalciferol substitution in the improvement of patients outcomes	Chronic lymphoid leukemia	Interventional; efficacy studies	Drug: Cholecalciferol	III
NCT02341495/09.2013	Theeffect of combinatorial therapy in complete remission and its durability	Acute myeloid leukemia	Interventional; efficacy studies	Drug: Oleum Neutralicum Drug: Deferasirox	II
NCT01748448/12.2012	To assess whether cholecalciferol supplementation after surgery of	Cutaneous malignant melanoma	Interventional; efficacy studies	Drug: Cholecalciferol Drug: Azacitidine Drug: Cholecalciferol 100,000 IU monthly	III

(*Continued*)

TABLE II. (*Continued*)

Study number/start date	Main goal of study	Type of cancer	Type of study	Intervention	Phase
	a first cutaneous malignant melanoma protects against relapse of the disease			Drug: Arachides Oleum Raffinatum	
NCT01588522/04.2012	Dose-escalation study, to evaluate the safety, tolerability and pharmacokinetics of a Topical compound 31543 (Calcitriol) in adult cancer patients receiving Taxane-based chemotherapy for the treatment of advanced or recurrent disease	Breast, cervical, endometrial, ovarian, primary peritoneal carcinoma, bone sarcoma, solid tumors	Interventional; safety studies	Drug: Calcitriol (compound 31543)	I
NCT01896804/07.2013	The side effects of calcitriol in preventing lung cancer in high risk patients	Squamous dysplasia (angiogenic), bronchial intraepithelial neoplasia, squamous metaplasia	Interventional; safety studies	Dietary supplement: Calcitriol	Pilot studies
NCT01608451/05.2012	Te effect of combinatorial therapy on disease-free survival rate and tumor response	Breast (large, operable)	Interventional; safety/ efficacy studies	Drug: Cholecalciferol 300,000 IU/ml, 4 cycles Drug: Progesterone 500 mg 4 cycles	III

Puigvert et al., 2016], topoisomerase inhibitors which block the ligation step of DNA replication, generating single and double stranded breaks [Xu and Her, 2015; Onodera et al., 2016], and nucleoside analogs such as Cytarabine (AraC) which disrupt normal DNA replication through incorporation into the extending DNA strands [Ewald et al., 2008].

Although the exact nature of DNA damage depends on many factors, including the nature of the external damaging agents or the endogenously arising compounds, the cell type, and stage of the cell cycle in which damage occurs, there is a commonality in the cells responses to this damage. There are three primary outcomes: the DNA may be restored to its native state without any adverse consequences, the attempted repair may be inaccurate, and result in a mutation or chromosomal aberration. Finally, if the damage is overwhelming or the repair machinery is compromised, the cell dies, usually by apoptosis or one of its variants [Matt and Hofmann, 2016].

It is outside the scope of this review to dissect the mechanisms which repair DNA damage caused by all agents, but in an outline, there are sensors of replication stress which accompany DNA damage, then transducers and effectors of the variable outcome [Zhou and Elledge, 2000]. These outcomes can be a cell cycle block, the enhanced transcription of factors necessary for repair, or as mentioned above, DNA repair with the alternative of cell death.

The primary event triggered by DNA damage is the recruitment of DNA damage signaling and repair proteins, collectively known as DNA Damage Response (DDR), which coordinates the induction of cell cycle check points with DNA repair, and movement of repair proteins to the sites of DNA damage [Cortez et al., 1999; Mills et al., 1999; Brown and Baltimore, 2000; Lim et al., 2000]. In most cells the principal sensors of DNA damage are ataxia-telangiectasia mutated (ATM) and Rad3-Related (ATR). These kinases initiate a cascade of phosphorylation events with Checkpoint 2 (Chk2) kinase a target of ATM and Chk1 a target of ATR, mediating cell cycle arrest [Ball et al., 2005; Ciccia and Elledge, 2010]. ATR is also primarily responsible for the phosphorylation of a histone variant known as H2AX, when phosphorylated known as gamma H2AX (γH2AX) in response to replication stress [Ward and Chen, 2001]. Double strand DNA breaks (DSBs) often result from replicative stress as well as from external damaging agents, replication fork collision, and γH2AX, massively accumulates at the chromatin sites surrounding DSBs [West and Bonner, 1980; Rogakou et al., 1999]. Thus, γH2AX serves as a valuable marker of DNA damage, both molecularly or visualized as nuclear foci. In addition, ATR can phosphorylate p53, BRCA1 and Rad17. These, and a plethora of other factors collectively inhibit DNA replication and mitosis, while promoting DNA repair or apoptosis. It is important to emphasize that the choice of apoptosis rather than continuing repair is not precisely understood in molecular terms: what is the key factor that makes DNA repair ineffective and the cell commits suicide?

POTENTIAL OF VDDs TO SIGNAL A SWITCH FROM DNA REPAIR TO APOPTOSIS

There are several suggestions in the current literature of signals which could switch DNA repair to apoptosis, though none have been previously related to vitamin D as a treatment option. Recently, a

model for repair/apoptosis switch has been advanced, which builds on the accumulated knowledge that following DNA damage Chk1 is an important suppressor of cell death [Rodriguez and Meuth, 2006; Sidi et al., 2008]. DNA damage-related replication stress triggers apoptosis in the absence of ATR-Chk1 function which slows down the S-phase progression by suppressing inappropriate firing of replications origins, and helps to maintain fork integrity (e.g. Maya-Mendoza et al. [2007]). Specifically, DNA replication fork stress generates single stranded DNA (ssDNA) which is coated by the Replication Protein A (RPA), and this activates the ATR-Chk1 pathway that leads to cell survival [Zou and Elledge, 2003]. However, based on studies of human colon cancer cells, it is proposed that pharmacological inhibition of Chk1 activity results in hyper-phosphorylation of RPA2 due, in part, to enhanced ATR activation and results in apoptosis [Zuazua-Villar et al., 2015]. Interestingly, Chk1 depletion also results in enhanced H2AX phosphorylation [Gagou et al., 2010]. In the Chk1-suppressed context, it was also proposed that the Death Domain (DD) protein PIDD can trigger pro-survival NF-κB signaling when its DD binds RIP1, but when the DD binds RAIDD it activates the pro-apoptotic caspase 2, and leads to cell death [Ando et al., 2012]. However, these studies did not make a clear molecular connection between replicative stress and apoptosis, and as yet have not been shown to have general applicability.

Another proposal for the switch from DNA repair to apoptosis posits that tyrosine 142 phosphorylation of H2AX modulates survival and apoptosis decisions. In this scenario, in addition to H2AX Ser139 phosphorylation which provides a docking site for DNA repair factors near the DSBs [Rogakou et al., 1999], Tyr 142 is also phosphorylated, but in contrast to Ser139 phosphorylation, it is gradually dephosphorylated following DNA damage [Stucki et al., 2005; Cook et al., 2009; Stucki, 2009; Xiao et al., 2009]. The switch depends on whether the repair factor Mediator of DNA Damage Checkpoint Protein 1 (MDC1), or the stress related MAP kinase JNK1 is recruited to H2AX. MDC1 binds to H2AX when only Ser139 is phosphorylated, while JNK1 binds when both Ser139 and Tyr 142 are phosphorylated. The latter leads to apoptosis in the system studied. Although the studies were not extensively expanded, the hypothesis provides a potential molecular mechanism for the apoptosis induction by JNK1 in many systems [Jia et al., 2014; Benzina et al., 2015; Ning and Du, 2015].

Since it is well established that VDDs upregulate JNK expression (e.g., [Ji et al., 2002; Wang et al., 2003, 2005a,b]) the above studies may provide a basis for future use of VDDs in cancer therapy. For instance, it has been reported that there is positive feedback signaling between ATM and VDR and this may be important for cancer chemoprevention [Ting et al., 2012]. Other examples include the cooperation of JNK pathway to trans-activate VDR and thus sensitize human breast cancer cells to VDD-induced growth inhibition [Qi et al., 2002], the activation of JNK which is associated with anti-proliferative actions of calcitriol in human osteosarcoma [Wu et al., 2007], and JNK has been reported to be involved in calcitriol-induced breast cancer death [Brosseau et al., 2010]. Of potentially more immediate application to treatment of human neoplastic disease is the recent report that cytotoxicity of AraC, the standard treatment for AML, is significantly enhanced by a VDD-based induction of differentiation [Wang et al., 2015a]. Thus, it seems that in human cells DNA repair is "badly treated" by vitamin D and analogs.

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