

Vitamin D for the prevention and treatment of pancreatic cancer

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$1\alpha,25(\text{OH})_2\text{D}_3$ and its analogs are potentially attractive novel therapies for pancreatic cancer.

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Abstract

Pancreatic cancer is ranked fifth among cancer-related deaths worldwide with a 5-year survival rate of less than 5%. Currently, surgery is the only effective therapy. However, most patients are diagnosed in the late stage and are not suitable for receiving curative surgery. Moreover, pancreatic cancer doesn't respond well to traditional chemotherapy and radiotherapy, leaving little effective treatment for advanced pancreatic cancer cases. $1\alpha,25$ -dihydroxyvitamin D_3 [$1\alpha,25(\text{OH})_2\text{D}_3$], the biologically active form of vitamin D_3 , was originally identified during studies of calcium and bone metabolism, though it is now recognized that it exerts biological effects in almost every tissue in the body. Abundant evidence has shown that $1\alpha,25(\text{OH})_2\text{D}_3$ has antiproliferative, apoptotic, pro-differentiation and antiangiogenesis effects in many types of cancer cells *in vivo* and *in vitro*, including breast, prostate, and colon. Similarly, the antitumor growth effect of $1\alpha,25(\text{OH})_2\text{D}_3$ on pancreatic cells has been demonstrated. The clinical use of $1\alpha,25(\text{OH})_2\text{D}_3$ is impeded by the lethal side effects of hypercalcemia and hypercalciuria. Therefore, $1\alpha,25(\text{OH})_2\text{D}_3$ analogs, which are either equipotent or more potent than $1\alpha,25(\text{OH})_2\text{D}_3$ in inhibiting tumor cell growth but with fewer hypercalcemic and hypercalciuric side effects, have been developed for the treatment of different cancers. Recently, a pre-clinical study demonstrated that a less calcemic analog of $1\alpha,25(\text{OH})_2\text{D}_3$, 19-nor- $1\alpha,25(\text{OH})_2\text{D}_2$ (Paricalcitol), is effective in inhibiting tumor growth *in vitro* and *in vivo*, via upregulation of p21 and p27 tumor suppressor genes. Studies on the anti-tumor effects of a more potent analog of Paricalcitol are underway.

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INTRODUCTION

Pancreatic adenocarcinoma is one of the most lethal human malignancies. It ranks as the fourth most common cancer-related mortality in the Western world and fifth most common worldwide^[1]. There were 37 680 new cases of pancreatic cancer and 34 290 deaths due to this disease in 2008 in the United States alone^[2]. The overall 5-year survival rate of pancreatic cancer is estimated to be around 1%-4%, which is attributed to its aggressive growth behavior, such as early local spread and metastasis, and resistance to radiation and most systemic chemotherapies^[1]. The poor prognosis is also due to the lack of effective early diagnosis. Consequently, most patients have been diagnosed with late stage disease. Currently, surgery remains the cornerstone of treatment. After resection, the 5-year survival rate is 10%-29%^[3-5], but only 10%-15% of pancreatic cancer patients are suitable candidates for resection. For the non-operable pancreatic cancer cases, the most frequently used treatment methods include radiation and chemotherapy with 5-fluorouracil, cisplatin or gemcitabine^[6-8], or a combination of these modalities^[9-11]. Growing evidence supports neoadjuvant therapy to downstage some pancreatic cancer patients from borderline resectable to resectable disease^[12,13],

but its impact on long-term survival still needs further examination^[14]. With this bleak background, there is an urgent need to develop novel treatments for pancreatic cancer.

SOURCES AND METABOLISM OF VITAMIN D

The production of vitamin D₃ depends on solar ultraviolet B radiation (wavelength between 290-315 nm), which converts 7-dehydrocholesterol stored in the skin to previtamin D₃. Previtamin D₃ is then thermoisomerized to vitamin D₃, which then enters the bloodstream and is bound to the vitamin D binding protein. Very little food naturally contains vitamin D. The cutaneous synthesis of vitamin D₃ is normally responsible for over 90% of our vitamin D requirement^[15]. Vitamin D (including both vitamin D₂ and vitamin D₃) obtained from sunlight or dietary sources is then converted to 25-hydroxyvitamin D [25(OH)D], catalyzed by vitamin D-25-hydroxylase in the liver. 25(OH)D is the major circulating form of vitamin D and is widely accepted as an index of vitamin D status in humans. However, it is biologically inert until it is hydroxylated in the kidney to form 1 α ,25-dihydroxyvitamin D [1 α ,25(OH)₂D]. 1 α ,25(OH)₂D is a lipid-soluble hormone that interacts with the vitamin D receptor (VDR) to exert a variety of functions, including genomic and non-genomic actions.

VITAMIN D AND CANCER

1 α ,25(OH)₂D, the biologically active form of vitamin D, was originally discovered because of its effects on calcium and bone metabolism. It is now recognized that the hormone has activities in almost every tissue in the body. 1 α ,25(OH)₂D₃ implements this effect through binding to the nuclear VDR and then binding to a specific DNA sequence, the vitamin D response elements (VDREs)^[16]. *Via* this genomic pathway, 1 α ,25(OH)₂D₃ can modulate gene expression in a tissue-specific manner, mainly leading to inhibition of cellular proliferation, induction of differentiation and apoptosis, which in turn, protect cells from malignant transformation and repress cancer cell growth.

However, the use of vitamin D to treat cancers has been impeded by lethal hypercalcemia induced by systemic administration of 1 α ,25(OH)₂D₃. To overcome this drawback, analogs of 1 α ,25(OH)₂D₃, exhibiting more potent growth inhibition but less calcemic effects, have been developed as anticancer drugs^[17], and some of them have shown great results in pre-clinical studies. For example, Akhter *et al*^[18] demonstrated that a 1 α ,25(OH)₂D₃ analog, EB 1089, exhibited an antiproliferative effect on colon cancer in a xenograft animal model. Abe-Hashimoto *et al*^[19] showed that another 1 α ,25(OH)₂D₃ analog, OCT, displayed an antitumor effect on a xenograft model using MCF-7, a

breast cancer cell line, in combination with tamoxifen. Furthermore, Polek *et al*^[20] showed that another analog, LG190119, possessed antiproliferative activity when tested in an LNCaP prostate cancer cell xenograft model.

There are some limited clinical trials that show 1 α ,25(OH)₂D₃ and its analogs have antitumor effects in humans when used alone or in combination with other chemotherapy drugs. For example, Beer *et al*^[21] conducted a phase II clinical trial in which they showed the combination of 1 α ,25(OH)₂D₃ and docetaxel could induce > 50% decline in PSA, a prostate cancer tumor marker, and improve survival of prostate cancer patients. However, most of the clinical trials only confirmed the less- or non-calcemic effect of 1 α ,25(OH)₂D₃ or its analog when used alone or in combination with other chemotherapy drugs without prolonging the survival of cancer patients. There are still many ongoing clinical trials attempting to demonstrate the antitumor effect of 1 α ,25(OH)₂D₃ and its analogs in humans. More effort is required in order to fully appreciate the clinical utilities of vitamin D-based therapies in treating human diseases, including cancers.

MECHANISMS OF VITAMIN D ACTIONS FOR CANCER TREATMENT

Vitamin D reduces the risk of cancer through its biologically active metabolite, 1 α ,25(OH)₂D₃, which regulates cellular proliferation and differentiation, inhibits angiogenesis, and induces apoptosis.

Stumpf *et al*^[22], in 1979, reported that the VDR existed not only in the intestine, bone and kidney, but in almost all tissues in the body. Suda *et al*^[23] (1982) first noted that 1 α ,25(OH)₂D₃ caused a marked inhibition of cell growth on VDR- positive M-1 leukemic cells. In the same year, Tanaka *et al*^[24] reported that 1 α ,25(OH)₂D₃ showed the same effect on HL-60 leukemic cells, which had the VDR. Since then, many VDR-containing cancer cell lines, including prostate, colon, breast, lung, and melanoma, have shown growth inhibition when exposed to 1 α ,25(OH)₂D₃^[15,25-27].

The antiproliferative effects of 1 α ,25(OH)₂D₃ are mainly due to alterations in several key regulators of the cell cycle, culminating in dephosphorylation of retinoblastoma protein and arrest of cells in G₀/G₁^[28]. Progression of the cell cycle is regulated by cyclins and their associated cyclin dependant kinases and cyclin dependant kinase inhibitors (CKIs). The CKI genes, such as p21 and/or p27, have VDRE within their promoter regions, and are genomic targets of the 1 α ,25(OH)₂D₃/VDR complex in many cell types, which in turn, induces G₁ cell-cycle arrest and withdrawal from the cell cycle^[29-31]. However, some genes are transcriptionally affected by 1 α ,25(OH)₂D₃ but lack VDREs in their promoter regions, which suggests that 1 α ,25(OH)₂D₃ induces indirect effects on cell-cycle regulation through another signaling pathway.

For example, $1\alpha,25(\text{OH})_2\text{D}_3$ could downregulate the expression of estrogen, epidermal growth factor, insulin-like growth factor 1, and keratinocyte growth factor and upregulate inhibitory growth factors, such as transformation growth factor- β ^[32-35].

$1\alpha,25(\text{OH})_2\text{D}_3$ can also induce differentiation to control tumor cell proliferation through the pathways of phosphatidylinositol 3-kinase, which is VDR dependent^[36], and by suppression of interleukin 12 protein secretion^[37], which is VDR independent.

Induction of apoptosis is another important function of $1\alpha,25(\text{OH})_2\text{D}_3$, which represses the expression of the antiapoptotic protein, BCL2, and prosurvival protein, BCL-XL. $1\alpha,25(\text{OH})_2\text{D}_3$ also enhances the expression of proapoptotic proteins such as BAX and BAD^[38]. In addition to the BCL2 family, $1\alpha,25(\text{OH})_2\text{D}_3$ can activate the caspase effector molecules directly to induce apoptosis^[38]. Furthermore, it has been shown that $1\alpha,25(\text{OH})_2\text{D}_3$, in combination with radiation or chemotherapeutic agents, causes an additive effect on cancer cell death^[39-42].

Inhibition of angiogenesis is also an important anticancer mechanism of $1\alpha,25(\text{OH})_2\text{D}_3$. $1\alpha,25(\text{OH})_2\text{D}_3$ can repress endothelial cell growth *in vitro* and reduce angiogenesis *in vivo*^[43-45]. The anti-angiogenic effects of $1\alpha,25(\text{OH})_2\text{D}_3$ might subsequently lead to the inhibition of metastasis, as demonstrated in murine prostate and lung models treated with $1\alpha,25(\text{OH})_2\text{D}_3$ ^[46,47].

The precise anticancer mechanisms of $1\alpha,25(\text{OH})_2\text{D}_3$, including VDR-dependent and VDR-independent pathways are not fully understood. For the further use of $1\alpha,25(\text{OH})_2\text{D}_3$ and its analogs in the treatment of cancers, there should be more studies addressing this issue to pave the way for the development of more potent $1\alpha,25(\text{OH})_2\text{D}_3$ analogs.

ASSOCIATION OF VITAMIN D AND PANCREATIC CANCER-EPIDEMIOLOGICAL EVIDENCE

Epidemiologic studies have shown that vitamin D status, influenced by living at high or low latitude, solar UV exposure and dietary intake of vitamin D, was inversely associated with the incidence of some cancers such as prostate, colon and breast^[48-50]. It was also reported that the risk of developing prostate, breast and colon cancer was decreased by 30%-50% if the serum concentration of 25(OH)D exceeded 50 nmol/L^[51,52]. Tangpricha *et al.*^[53] demonstrated that vitamin D deficiency enhanced the growth of MC-26 colon cancer xenografts in BALB/c mice, which supported the hypothesis that vitamin D sufficiency could reduce the proliferation of tumor cells *in vivo*.

To date, there have been only two epidemiological studies discussing the vitamin D status and the incidence of pancreatic cancer. One was conducted by Skinner *et al.*^[54] on U.S. nurses and health professionals, which demonstrated that higher dietary intake of vitamin D could be associated with lower incidence of pancreatic

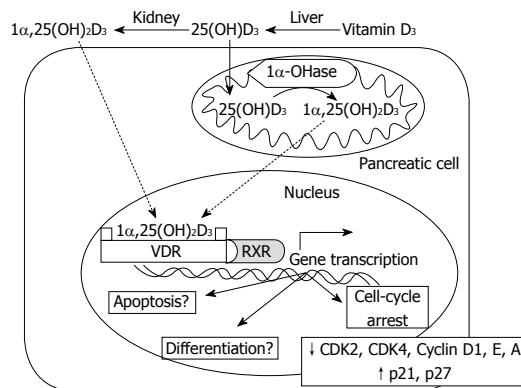


Figure 1 Mechanisms of Vitamin D₃ action on pancreas cells. Both $1,25(\text{OH})_2\text{D}_3$ and $25(\text{OH})\text{D}_3$ can enter pancreas cells, where $25(\text{OH})\text{D}_3$ can be converted to $1,25(\text{OH})_2\text{D}_3$ by $1\alpha\text{-OHase}$. $1,25(\text{OH})_2\text{D}_3$ can bind the VDR and further combine with the retinoid X receptor (RXR) to form a heterodimer, VDR-RXR. The VDR-RXR heterodimer binds to specific vitamin D response elements located in the promoter region of vitamin D-responsive genes, which in turn induces gene transcription. So far, in terms of pancreas cells, inhibition of CDK2, CDK4, Cyclin D1, Cyclin E, Cyclin A and upregulation of p21 and p27 have been demonstrated, leading to a block in the cell cycle at G₀/G₁. Regarding induction of differentiation, apoptosis and other anticancer mechanisms, further studies are required.

cancer. The other report, however, conducted in the observational cohort of the Finnish Alpha-Tocopherol Beta-Carotene (ATBC) trial, showed a discrepancy in results compared to the report by Skinner *et al.*^[54]. The ATBC data suggested that a higher serum concentration of 25(OH)D in male smokers was associated with a higher incidence of pancreatic cancer^[55]. The reason behind these contradictory results was not clear, but they employed different measures of dietary intake of vitamin D *versus* 25(OH)D, and the participants in the ATBC trials were all male smokers, which might have contributed to the different conclusions in the two studies. To clarify this, more studies addressing the relationship between vitamin D status and incidence of pancreatic cancer are required.

VITAMIN D AND PANCREATIC CANCER-BIOCHEMICAL EVIDENCE

While the precise anticancer mechanisms, including VDR-dependent and VDR-independent actions, induced by $1\alpha,25(\text{OH})_2\text{D}_3$ still require further investigation, it is known that in pancreatic cancer cells, $1\alpha,25(\text{OH})_2\text{D}_3$ induces the expression of p21 and p27 and inhibits the production of cyclins (D₁, E and A) and cyclin dependent kinases 2 and 4, which in turn, elicit cell cycle arrest in G₀/G₁ *in vitro*^[56]. Similar effects have been observed with 19-nor- $1\alpha,25(\text{OH})_2\text{D}_2$ (Paricalcitol) in human pancreatic cancer cells *in vitro* and *in vivo* by upregulating the expressions of p21 and p27^[57] (Figure 1).

Currently, very little is known about the mechanisms of vitamin D actions on pancreatic cancer cells. More emphasis in this area is needed, because very few efficient therapeutic options are available to benefit pancreatic cancer survival.

POTENTIAL OF VITAMIN D ANALOGS FOR PANCREATIC CANCER TREATMENT

Since the VDR exists in almost every tissue of the body^[22] and $1\alpha,25(\text{OH})_2\text{D}_3$ exhibits growth inhibitory effects on many different types of cancer cells, several studies have been performed to investigate the anticancer effect of vitamin D and its analogs on pancreatic cancer cells during the past two decades. For example, Kawa *et al*^[56] reported that 22-oxa- $1\alpha,25(\text{OH})_2\text{D}_3$, a $1\alpha,25(\text{OH})_2\text{D}_3$ analog, caused growth inhibition in three pancreatic cancer cell lines and inhibited the growth of a BxPC-3 tumor in a xenograft nude mice model^[58]. Colston *et al*^[59] demonstrated that another $1\alpha,25(\text{OH})_2\text{D}_3$ analog, EB 1089, exhibited more potent antitumor effects than $1\alpha,25(\text{OH})_2\text{D}_3$ on the GER cell line, a human pancreatic cancer cell line, *in vitro* and *in vivo*. Pettersson *et al*^[60] also reported that EB 1089 induced greater tumor growth inhibition than 9-cis-retinoic acid *in vitro*. These two pre-clinical studies therefore suggested that EB 1089 might be a promising vitamin D analog for further clinical trials in pancreatic cancer patients. However, in a phase II clinical trial, which is also the only clinical trial studying the use of vitamin D analogs against pancreatic cancer, EB 1089 given once daily orally failed to significantly improve patient survival, although most patients tolerated the daily orally dose of 10-15 μg of the drug well, without causing hypercalcemia^[61].

With the knowledge that 19-nor- $1\alpha,25(\text{OH})_2\text{D}_2$ (Paricalcitol) is a Federal Drug Administration approved drug for the treatment and prevention of secondary hyperparathyroidism associated with chronic kidney disease^[62], and this analog has comparable growth inhibitory effects as $1\alpha,25(\text{OH})_2\text{D}_3$ in human prostate cancer cells *in vitro*^[63], Schwartz *et al*^[57] studied the same analog in human pancreatic cancer cells *in vitro* and demonstrated that it also inhibited the proliferation of these cells. Given the fact that Paricalcitol has been shown to be less calcemic than $1\alpha,25(\text{OH})_2\text{D}_3$ and few therapeutic options for pancreatic cancer patients are available, it is worth further exploration as an anticancer drug for pancreatic cancer.

In addition to using synthetic $1\alpha,25(\text{OH})_2\text{D}_3$ analogs to treat pancreatic cancer in an effort to avoid hypercalcemia, another strategy is the employment of inactive prohormone $25(\text{OH})\text{D}_3$ (Figure 1). This is based on the finding that many normal and cancerous cells, including prostate cell lines and primary cultures of prostate cells, possess $25(\text{OH})\text{D}_3$ - 1α -hydroxylase (1α -hydroxylase or CYP27b1), the enzyme responsible for the conversion of $25(\text{OH})\text{D}_3$ to $1\alpha,25(\text{OH})_2\text{D}_3$ ^[26], and CYP27b1 has been proposed as a tumor suppressor^[64]. Furthermore, it has been demonstrated that $25(\text{OH})\text{D}_3$ had a comparable tumor growth inhibitory effect to $1\alpha,25(\text{OH})_2\text{D}_3$ on primary cultures of prostate cells^[63,65]. These findings led to a subsequent study demonstrating that CYP27b1 activity was also expressed in pancreatic cancer cells and the growth of these cancer cells was

inhibited in the presence of $25(\text{OH})\text{D}_3$ ^[66]. Given the fact that the conversion of $25(\text{OH})\text{D}_3$ to $1\alpha,25(\text{OH})_2\text{D}_3$ occurs within the cell, and the $1\alpha,25(\text{OH})_2\text{D}_3$ formed acts in an autocrine/paracrine fashion^[26,63-65], systemic administration of $25(\text{OH})\text{D}_3$ might greatly minimize the risk of hypercalcemia. $25(\text{OH})\text{D}_3$ has been approved by the Federal Drug Administration to treat vitamin D deficiency in humans; therefore, $25(\text{OH})\text{D}_3$ could be another attractive candidate for clinical trials in pancreatic cancer patients.

CONCLUSION

Abundant evidence indicates that $1\alpha,25(\text{OH})_2\text{D}_3$ has antiproliferative, pro-differentiative, apoptotic and antiangiogenic activities in different types of tumor cells. In different cancer cell types, $1\alpha,25(\text{OH})_2\text{D}_3$ can induce the expression of various molecular markers to regulate cell growth. Even in the same tissue, different cell types might exhibit heterogeneous responses to the addition of $1\alpha,25(\text{OH})_2\text{D}_3$. It is known that $1\alpha,25(\text{OH})_2\text{D}_3$ and its analogs can inhibit pancreatic cancer cell growth *in vitro*^[56,59] via activation of p21 and p27, which in turn influence cell cycle progression and arrest cells in G_0/G_1 . So far, the only pancreatic cancer clinical trial using a $1\alpha,25(\text{OH})_2\text{D}_3$ analog, EB 1089^[61], did not show significant prolongation of survival. However, a preclinical study with 19-nor- $1\alpha,25(\text{OH})_2\text{D}_2$ (Paricalcitol) in pancreatic cancer cells^[60] has provided some encouraging results and might lead to further clinical trials. Moreover, given the fact that pancreatic cancer cells possess 1α -hydroxylase (CYP27b1) activity and can convert the prohormone $25(\text{OH})\text{D}_3$, which has a low risk of inducing hypercalcemia even at high concentrations, into $1\alpha,25(\text{OH})_2\text{D}_3$ within the cells and thereby inhibiting pancreatic cancer cell growth in an autocrine/paracrine fashion^[26,63-65], prohormone $25(\text{OH})\text{D}_3$ -based therapy might be another attractive treatment strategy for pancreatic cancer in the future.

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