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Vitamin D for the Prevention and Treatment of Pancreatic Cancer

Kun-Chun Chiang¹ and Tai C. Chen²

¹*Chang Gung Memorial Hospital and Chang Gung University,*

²*Boston University School of Medicine,*

¹*Taiwan*

²*USA*

1. Introduction

Pancreatic adenocarcinoma (PCA), although infrequent, is one of the most lethal human malignancies. PCA ranks fourth in the Western countries and sixth worldwide among the most common cancer-related mortality based on GLOBOCAN 2008 (Jemal et al. 2011). Worldwide, an estimated 277,000 new cases of PCA were diagnosed in 2008 (Ferlay et al. 2008). In 2011, 44,000 new cases of PCA will be identified and 37,700 individuals will die from this disease in the US (Siegel et al. 2011). The nearly 1:1 ratio of incidence to mortality clearly implicates a poor prognosis and the lethal nature of PCA, which is the result of the difficulty of early diagnosis, early local spread, distant metastasis and resistance to traditional chemotherapy and radiotherapy. The overall five-year survival rate is estimated to be within the range of 1–4%, much lower than that of other types of cancers (Jemal et al. 2011). Up to the present time, the standard treatment for PCA is surgical extirpation, which may improve the overall five-year survival rate to 10–29% (Trede et al. 1990; Nitecki et al. 1995; Yeo et al. 1997). However, 40% of PCA patients already had distant metastasis at the time of diagnosis and another 40% were diagnosed with locally advanced cancer (Haller 2003; Jemal et al. 2011; Siegel et al. 2011), excluding them from being good candidates for resection.

Although the definite causes of pancreatic cancer are still poorly understood, several environmental risk factors have been implicated. Abundant epidemiological studies have indicated that the use of tobacco increases the risk of pancreatic cancer (Raimondi et al. 2009) and increased incidence of pancreatic cancer is positively associated with frequency and length of tobacco exposure (Hassan et al. 2007). A recent study based on a pooled analysis also concludes smoking is associated with an 18% increased risk of PCA (Lynch et al. 2009). On the other hand, the risk of PCA would dwindle after cessation of cigarette smoking for 10 years or longer (Iodice et al. 2008). Although alcohol has been related to increased risk of several types of cancers, the exact relationship between alcohol and PCA has not been established yet (Rohrmann et al. 2009; Jiao et al. 2009). A pooled analysis of 14 cohort studies reported a positive relationship between pancreatic cancer and women consuming more than 30 g of alcohol per day (Genkinger et al. 2009). A recent meta-analysis study also indicates that a 22% increased risk of PCA is observed in subjects with heavy

alcohol consumption (> 30g/day) (Tramacere 2010). High caloric intake and obesity are also identified to be risk factors for PCA (Reeves et al. 2007; Fryzek et al. 2005; Patel et al. 2005; Berrington de Gonzalez et al. 2003). While natural, plant-produced antioxidants, such as some flavonoids, are thought of traditional lys protective factors for some cancers, their roles in PCA are still not established (Nothlings et al. 2007). Fruits and vegetables also failed to offer definitive protective benefit for PCA in a large-scaled cohort study (Vrieling et al. 2009). Other risk factors, such as intake of coffee, use of aspirin, previous cholecystectomy, and history of diabetes or chronic pancreatitis, although less conclusive, may contribute to pancreatic cancer as well (Batty et al. 2009; Landi 2009; Lowenfels & Maisonneuve 2006).

While investigating the incidence of PCA in different locations, a geographical variation has been observed; that is in the northern latitudes, the incidence of pancreatic cancer is three- to four-times higher than that in areas closer to equator (Curado et al. 2007). This finding has been attributed to sunlight or ultraviolet (UVB) exposure, which is directly related to vitamin D synthesis and the main determinant of vitamin D status in humans. In this regard, abundant epidemiologic studies have shown that vitamin D status is inversely associated with the incidence of some cancers such as prostate, colon and breast (Garland & Garland 1980; Gorham et al. 1990; Schwartz & Chen 2005).

Recently, due to the dismal outcome of PCA treatments and resistance of PCA to available chemotherapy and radiotherapy, some new regimens or strategies have been developed. In this chapter, we describe the recent findings on the relationship between sunlight, vitamin D and pancreatic cancer incidence, the potential role of vitamin D analogues for the prevention and treatment of pancreatic cancer, and the metabolism and functions of vitamin D as well as a brief history of vitamin D.

2. Current treatment of pancreatic cancer

Currently, the standard treatment for resectable pancreatic cancer remains surgery, including radically resection of the primary tumor, surrounding tissues, as well as neighboring lymph nodes. However, as described above, only 20% of PCA patients are suitable candidates for operation when diagnosed with PCA (Haller 2003; Jemal et al. 2011; Siegel et al. 2011). After operation, adjuvant chemotherapy with either gemcitabine or a combination of fluorouracil and leucovorin is able to improve progression-free period and overall survival (Neoptolemos et al. 2004; Oettle et al. 2007; Regine et al. 2008). Combination of adjuvant chemotherapy and radiation therapy seems to increase overall survival; however, the results are not impressive (Herman et al. 2008). For unresectable pancreatic cancer, the principle of treatment is mainly palliative. The standard chemotherapy for this group of patients is gemcitamine alone (Renouf & Moore 2010). Once gemcitamine fails to provide benefit in this group of patients, according to National Comprehensive Cancer Network guidelines, capecitabine, FOLFOX, or a combination of capecitabine and oxliplatin should be considered (National Comprehensive Network guidelines 2008). It has been reported that in general PCA patients who respond poorly to the first line therapy may have an unfavorable response to the second line therapy as well (Herrmann et al. 2007). Recently, target therapy has gained attention for the treatment of certain cancers. However, at the present time, no suitable target therapy is available against PCA. Under these bleak conditions, the development of new therapies to treat PCA should be one of the priorities in cancer research.

3. History of vitamin D

The discovery of vitamin D is closely associated with the disease rickets. Rickets was prevalent in the 17th century when two English physicians, Daniel Whistler and Francis Glisson described this deformity of bone in 1645 and 1650, respectively (Hess 1929). It was not until 1822, Sniadecki made an important observation relating the prevalence of rickets to locations of residence; lower incidence of rickets was found among children living on farms than children living in the city of Warsaw, Poland (Mozolowski, 1939). In 1889, Theodore Palm, a medical missionary and epidemiologist, reported that children living near the equator did not suffer from rickets and, thus, suggested sunbathing as a possible cure and strategy for rickets prevention (Palm 1890). Both of them attributed their finding of geographic differences in rickets incidence to varied exposures to sunlight. In 1919, Edward Mellanby successfully made dogs rachitic by keeping them indoors and feeding them with oats exclusively, followed by curing this disease with cod liver oil (Mellanby 1919). During that period, cod liver oil was used to treat night blindness and fracture. Mellanby did not know at that time whether the cure of rickets was attributed to the newly discovered vitamin A present in cod liver oil (McCollum et al., 1916) or another substance within. It was not until 1922 that McCollum clearly demonstrated that the anti-rachitic substance present in cod liver oil was a new substance and named it "vitamin D" (McCollum 1922). Around the same period, Huldshinsky in 1919 discovered that sunlight exposure could cure rachitic children (Huldshinsky 1919). Subsequently, there seemed to be a relationship between the cure of rickets by sunlight exposure and vitamin D in the cod liver oil. Steenbock and Black (1924) and Hess and Weinstock (1924) then noted independently that UV-irradiated food could cure rickets, which suggested that UV light was capable of transforming one substance stored in food to cure rickets. In other words, UV irradiation could produce vitamin D, which was responsible for the anti-rachitic activity found in food.

Vitamin D was believed as biologically active for decades until DeLuca's laboratory showed that injected radioactive vitamin D₃ disappeared instantly in the circulation of rats and the label appeared again later in the blood. The major radioactive compound in the blood was isolated and tested for its ability in stimulating intestinal calcium transport (Norman et al. 1964). His group reported that this unknown compound acted much quicker and had higher activity than the parent substance vitamin D₃ (Morii et al. 1967), suggesting that vitamin D₃ might be further metabolized to become active. Subsequently, the unknown compound was isolated in pure form and identified as 25-hydroxyvitamin D₃ [25(OH)D₃] in 1968 (Blunt et al. 1968). Later, when radioactive 25(OH)D₃ was synthesized and injected into rats, several more polar metabolites were found and isolated. One of them was shown to stimulate intestinal calcium transport much quicker and to a greater extent than 25(OH)D₃. The compound was identified in 1971, independently by three groups of researchers as 1 α ,25-dihydroxyvitamin D₃ [1 α ,25(OH)₂D₃] (Lawson et al. 1971; Norman et al. 1971; Holick et al. 1971).

Vitamin D₃ (cholecalciferol) can be obtained either from the diet, including supplements, or synthesized in the skin from the precursor 7-dehydrocholesterol (7-DHC) via sunlight exposure (wave length: 290-315 nm). Vitamin D₃ is then bound to vitamin D binding protein (DBP) and circulates in the blood. After entering the liver, vitamin D₃ is hydroxylated by vitamin D-25-hydroxylase (25-OHase, mainly CYP2R1) to generate the circulating prohormone 25(OH)D₃, which has the highest affinity for DBP and is bound to DBP

in the circulation. The subsequent conversion of 25(OH)D₃ to the active form, 1 α ,25-dihydroxyvitamin D₃ [1 α ,25(OH)₂D₃], occurs in the kidneys and is catalyzed by a tightly regulated enzyme 25(OH)D-1 α -hydroxylase (1 α -OHase or CYP27B1). The active form then will be bound to DBP in the circulation and transported to its target organs, tissues and cells to induce gene transcription, including the up-regulation of *CYP24A1* as shown in Figure 2. The activation of 25(OH)D₃ may also take place in many extra-renal tissues, including pancreas, bone, breast, colon, prostate. The extra-renal synthesis of 1 α ,25(OH)₂D may explain why serum 25(OH)D level, instead of the circulating level of the active form, 1 α ,25(OH)₂D, is the index of vitamin D nutritional status. 1 α ,25(OH)₂D₃, either obtained from the circulation or within the cells in an autocrine fashion, will be hydroxylated by CYP24A1 (or 24-OHase) to form 1 α ,24,25-trihydroxyvitamin D₃ [1 α ,24,25(OH)₃D₃], the first step to inactivate 1 α ,25(OH)₂D₃, leading to the formation of calcitroic acid, which is water-soluble and is secreted in the urine.

4. Sources and metabolism of vitamin D

Two major forms of vitamin D exist in nature: vitamin D₂ and vitamin D₃. Commonly, vitamin D₂ (ergocalciferol) is produced from ergosterol of yeast and vitamin D₃ (cholecalciferol) is synthesized from 7-dehydrocholesterol (7-DHC) of lanolin. Vitamin D (representing D₂ and D₃) is rare in foods, only few foods contain sufficient vitamin D naturally (Chen et al. 2010). Therefore, fortification of vitamin D in foods, like orange juice, cheese, cereal and milk, is becoming popular in some countries. For most humans, exposure to sunlight remains the major source, accounting for about 90% of vitamin D requirement (Chen et al. 2010) (Figure 1). The basal and suprabasal layers of human skin contain 7-DHC, which can be converted to pre-vitamin D₃ as the skin receives UV irradiation (wavelength 290–315 nm). Pre-vitamin D₃ is further thermoisomerized to vitamin D₃ in the skin. Vitamin D, obtained from food (may contain vitamin D₂ and/or vitamin D₃) or synthesized from skin after exposure to sunlight, enters the blood circulation carried by vitamin D binding protein (DBP). Upon entering the liver, vitamin D is hydroxylated at the C-25, catalyzed by vitamin D-25-hydroxylase (25-OHase) (Schuster 2011), to produce 25(OH)D₃. 25(OH)D is further hydroxylated by the enzyme 1 α -OHase or CYP27B1 mainly in the renal proximal tubules at the C-1 position to form the active metabolite, 1 α ,25(OH)₂D₃. While 1 α ,25(OH)₂D₃ is the active form and is responsible for the various biological activities exerted by vitamin D₃, 25(OH)D₃ is the major circulating form of vitamin D₃ and is considered as the most reliable index of vitamin D nutritional status. 25(OH)D₃ has the highest affinity for DBP and circulates as a DBP-bound form in the blood stream. Another renal enzyme, which also plays a crucial role in vitamin D metabolism, is 25(OH)D-24-hydroxylase (24-OHase or CYP24A1). CYP24A1 is responsible for the degradation of 1 α ,25(OH)₂D₃, forming 1 α ,24,25(OH)₃D₃, and thus terminating the actions of 1 α ,25(OH)₂D₃. In addition, when there is an excess of 25(OH)D₃, 24-OHase in the kidneys is capable of converting it into 24,25(OH)₂D₃ to prevent the over-production of 1 α ,25(OH)₂D₃ (Schuster 2011). Of note, originally it was believed that CYP27B1 and CYP24A1 exist exclusively in the kidneys, the two enzymes have been found to express in many extra-renal tissues (Zehnder et al. 2001; Chen & Holick 2003; Schwartz et al. 2004; Kemmis et al. 2006; Chiang & Chen 2009), including the pancreas. Given that anephric individuals have no detectable 1 α ,25(OH)₂D₃ in their circulation, it is believed that extrarenal-generated 1 α ,25(OH)₂D₃ acts and is degraded only locally in an autocrine and paracrine manner. This autocrine/paracrine pathway seems

to be regulated in a tissue-specific manner and is not associated with systemic calcium homeostasis. Based on this theory, once 25(OH)D₃ is internalized into the cells, the fate of 25(OH)D₃ may depend on the relative expression levels of CYP27B1 to CYP24A1. In the cells with dominant expression of CYP27B1, 25(OH)D₃ will be converted to 1 α ,25(OH)₂D₃ to exert its cellular functions. Meanwhile, the locally generated 1 α ,25(OH)₂D₃ will up-regulate the expression of CYP24A1 within the cells to hydroxylate 1 α ,25(OH)₂D₃ and excess 25(OH)D₃ to form their respective 24-hydroxylated metabolites leading to their catabolism. On the other hand, in cells dominated with the expression of CYP24A1, the generated 1 α ,25(OH)₂D₃ will be degraded very quickly with little or no chance to exert biological actions (Ly et al. 1999; Schuster 2011).

5. Functions of vitamin D

The genomic action of 1 α ,25(OH)₂D₃ is mediated through its binding to vitamin D receptor (VDR) to modulate various gene expressions in a cell- and tissue- specific manner (Norman 2006) (Figure 2). VDR is a member of the nuclear receptor superfamily and is expressed in almost all tissues (Hausler et al. 1997). To date, 1 α ,25(OH)₂D₃ has been well described to exert anti-proliferation, anti-inflammation, pro-differentiation, pro-apoptosis and immune regulation in a tissue- and cell-specific manner (Chiang & Chen 2009; Bikle 2009; Adams & Hewison 2010). So far, more than 2770 VDR binding sites have been identified within 229 vitamin D-regulated genes as shown by a Chip-sequencing method (Ramagopalan et al. 2010). Many cancer cell lines, including prostate, lung, liver, breast, pancreas and liver cancers, have been shown to express VDR, and 1 α ,25(OH)₂D₃ has been found to have growth inhibitory effect on these cells (Colston et al., 1980; Skowronski et al., 1993; Hulla et al., 1995; Chen & Holick 2003; Flanagan et al., 2009; Chiang et al., 2009).

The active form of vitamin D₃, 1 α ,25(OH)₂D₃, either synthesized in an autocrine fashion or obtained from the kidneys, exerts its genomic effects by binding to the VDR/retinoid X receptor (RXR) complex on vitamin D response element (VDRE) in the promoter region of vitamin D-regulated genes. The transcriptional effects include cell cycle arrest, pro-differentiation, pro-apoptosis, anti-inflammation, regulation of immune response and *etc.* After 1 α ,25(OH)₂D₃ elicits its function, it is then inactivated by CYP24A1. Since many tissues possess CYP27B1 and CYP24A1 simultaneously, the internalized 25(OH)D₃ can be activated or inactivated to form 1 α ,25(OH)₂D₃ or 24-25(OH)D₃ based on the expression rates of 1 α -OHase to 24-OHase.

Once 1 α ,25(OH)₂D₃ is internalized into cells, it binds to VDR. The liganded VDR then form a heterodimer with RXR and binds to VDRE (Tsai & Omalley 1994) located in the promoter regions of vitamin D responsive genes to modulate the gene expression. In cancer cells, the action mainly leads to the inhibition of cancer growth and the prevention of cancer cells from invading to surrounding normal tissues. Mechanistically, the genomic pathways are regulated by multiple co-factors (Hausler et al. 1998). The VDR conformational change occurs upon 1 α ,25(OH)₂D₃ binding to VDR, leading to subsequent phosphorylation, and gives rise to the release of co-repressors and the recruitment of co-activators (Tagami et al. 1998; Li et al. 2007). In addition to the genomic pathways, 1 α ,25(OH)₂D₃ has been shown to be able to induce instant biologic reaction at the plasma membrane or in the cytoplasm by changing transmembrane signals quickly (Norman 2006).

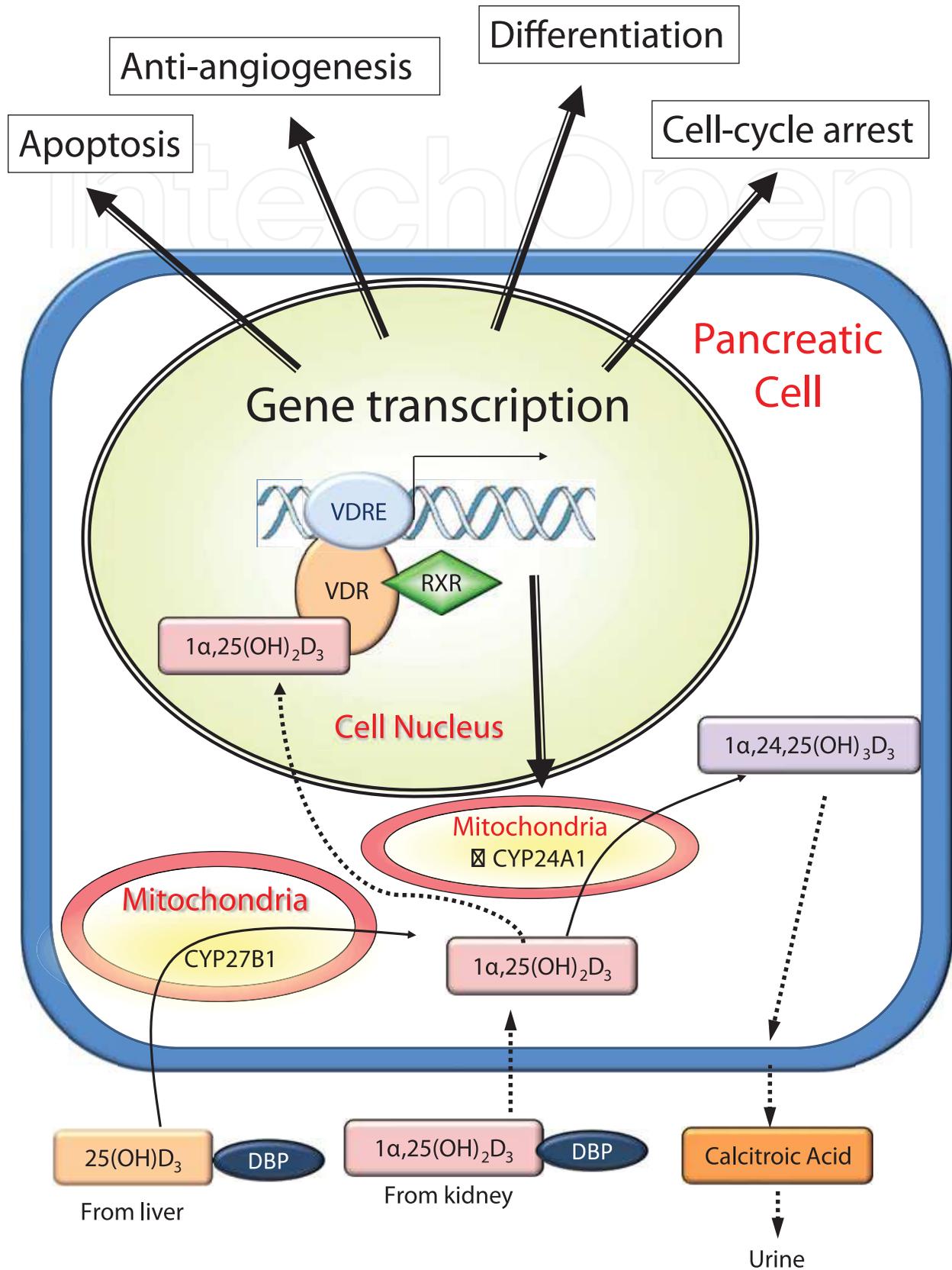


Fig. 2. Functions of vitamin D in pancreatic cells

This kind of action does not influence gene expression directly, though, its cross-talk with varied signaling pathways still can modulate gene transcription (Losel & Wehling 2003). To date, the exact mechanisms for non-genomic actions of $1\alpha,25(\text{OH})_2\text{D}_3$ are not well understood. Nevertheless, the existence of non-classical membrane VDR has been found to be related to the rapid actions (Huhtakangas et al. 2004), including activation of protein kinase C and protein phosphatase PP1c. The actions have been shown to result in subsequent ion channel activity modulation (Bettoun et al. 2002; Shah et al. 2006), which is also implicated in the growth inhibition of cancer cells.

6. Vitamin D and pancreatic cancer- biological studies

To date, $1\alpha,25(\text{OH})_2\text{D}_3$ has been shown to possess anti-tumor activity in many cancer cells expressing VDR through its anti-proliferative, pro-apoptotic, and pro-differentiation actions in a cell- and tissue-specific manner. In terms of pancreatic cancer, $1\alpha,25(\text{OH})_2\text{D}_3$ has been demonstrated to up-regulate the expression of p21 and p27 and down-regulate the expression of cyclins A, D₁, and E and cyclin dependent kinases 2 and 4, leading to cell cycle arrest at G₀/G₁ phase (Kawa et al. 1997). However, $1\alpha,25(\text{OH})_2\text{D}_3$ is known to cause hypercalcemia and hypercalciuria side effects when administered systemically. To overcome these lethal side effects caused by systemic administration of $1\alpha,25(\text{OH})_2\text{D}_3$, thousands of $1\alpha,25(\text{OH})_2\text{D}_3$ analogues have been synthesized in an effort to potentiate its anti-tumor effect while decreasing its hypercalcemic activity. Some of them have been found to induce greater cell-cycle arrest, differentiation, and/or apoptosis on pancreatic cancer cells *in vitro* and to inhibit tumor growth in the xenograft animal model. For example, 22-oxa- $1\alpha,25(\text{OH})_2\text{D}_3$ has been reported to cause growth inhibition on three pancreatic cancer cell lines and to inhibit xenografted BxPC-3 cell growth *in vivo* (Kawa et al. 1996). Similarly, EB-1089, a well-studied $1\alpha,25(\text{OH})_2\text{D}_3$ analogue, has been shown to inhibit pancreatic cancer growth *in vitro* and *in vivo* (Colston et al. 1997; Pettersson 2000), and has been investigated in a phase II clinical trial to treat advanced pancreatic cancer. While EB-1089 failed to prolong the survival of patients significantly in this trial (Evans et al. 2002), $1\alpha,25(\text{OH})_2\text{D}_3$ (0.5 $\mu\text{g}/\text{kg}$) in a combination with docetaxel successfully increased the period of time-to-progress of pancreatic cancer in a recently published phase II study enrolling 25 advanced pancreatic cancer patients as compared to treatment with docetaxel alone (Blanke et al. 2009). Several new analogues have been shown to possess promising results in *in vitro* studies. For example, a VDR-alkylating derivative of $1\alpha,25(\text{OH})_2\text{D}_3$, $1\alpha,25$ -dihydroxyvitamin D₃-3-bromoacetate ($1\alpha,25(\text{OH})_2\text{D}_3$ -3-BE), was able to inhibit pancreatic cancer cell growth at a lower concentration and to a greater extent than $1\alpha,25(\text{OH})_2\text{D}_3$, especially in combination with 5-amino-imidazole-4-carboxamide-1-beta-4-ribofuranoside (AICAR) (Persons et al. 2010). In another study, 19-nor- $1\alpha,25(\text{OH})_2\text{D}_2$ (Paricalcitol), which has been approved by the Food and Drug Administration for treating secondary hyperparathyroidism, has been demonstrated to have comparable growth inhibition as $1\alpha,25(\text{OH})_2\text{D}_3$ in pancreatic cancer *in vitro* and *in vivo* (Schwartz et al. 2008). Given that 19-nor- $1\alpha,25(\text{OH})_2\text{D}_2$ and 19-nor- $1\alpha,25(\text{OH})_2\text{D}_3$, are less calcemic analogues of $1\alpha,25(\text{OH})_2\text{D}_3$, we have studied a carbon-2 modified analogue of 19-nor- $1\alpha,25(\text{OH})_2\text{D}_3$, 19-nor-2 α -(3-hydroxypropyl)- $1\alpha,25(\text{OH})_2\text{D}_3$ or MART-10, in pancreatic cancer cells *in vitro* and found to be 100-1000 times as potent as $1\alpha,25(\text{OH})_2\text{D}_3$ to inhibit tumor cell growth. Most importantly, MART-10 does not increase serum calcium in rats (Iglesias-Gato, D. et al, 2011). Furthermore, MART-10 has been shown

to be a poor substrate of CYP24A1 and has a lower binding affinity for DBP compared to $1\alpha,25(\text{OH})_2\text{D}_3$, suggesting that this analogue is likely more bio-available than $1\alpha,25(\text{OH})_2\text{D}_3$ in circulation (Flanagan et al. 2009). Thus, MART-10 is a promising compound to treat pancreatic cancer.

7. Epidemiological evidence associating vitamin D and pancreatic cancer

Circulating vitamin D level, primarily determined by solar UVB exposure and partially influenced by food uptake and oral vitamin D supplementation, has been shown to be inversely associated with the incidence of many cancers, including prostate, colon and breast cancers in a number of epidemiological studies (Garland & Garland 1980; Gorham et al., 1990; Schwartz & Chen 2005). Garland et al. (2009) further reported that 58,000 new cases of breast cancer and 49,000 new cases of colon cancer could be prevented annually through vitamin D supplement. In addition, recent studies applying Hill's criteria for causality also clearly showed that UVB exposure and vitamin D status are negatively associated with cancer risk (Grant 2009; Grant & Boucher 2009). For pancreatic cancer, its exact relationship to vitamin D status has not been well understood. Although two earlier epidemiologic studies published in 2006 showed inconsistent findings about the relationship between pancreatic cancer incidence and serum 25(OH)D level (Skinner et al. 2006; Stolzenberg-Solomon et al. 2006), the death rate of pancreatic cancer has been shown to be inversely related to sun exposure (Mizoue 2004; Boscoe & Schymura 2006; Grant 2007; Tuohimaa et al. 2007). More recently, Stolzenberg-Solomon *et al.* (2010) conducted two pooled nested case control studies to investigate the potential association of vitamin D status and pancreatic cancer, and reported that the circulating 25(OH)D concentration was not related to the risk of pancreatic cancer. Furthermore, Stolzenberg-Solomon et al. showed that a high 25(OH)D level, exceeding 100 nmol/L (40 ng/mL), increased pancreatic cancer incidence two folds (odds ratio = 2.12, 95% confidence interval: 1.23, 3.64) (Stolzenberg-Solomon et al. 2010). However, they did find subjects with lower estimated annual residential solar UVB exposure would have higher risk of pancreatic cancer (Stolzenberg-Solomon et al. 2009). The reason behind the lack of association between serum levels and pancreatic cancer and other cancers maybe that serum 25(OH)D levels were only measured at one time point years prior to diagnosis of pancreatic cancer and, in fact, 25(OH)D levels change from season to season. For this reason, Yin *et al.* (2010) conducted case-control studies with zero lag time between diagnosis and serum 25(OH)D measurement, not nested studies, and found an inverse correlation between serum 25(OH)D level and breast cancer. Mohr SB *et al.* (2010) also demonstrated an inverse association between UVB irradiation and incidence rates of pancreatic cancer worldwide. They found that the incidence rate of pancreatic cancer was only half in countries with estimated serum 25(OH)D > 30 ng/ml as compared to those with serum 25(OH)D ≤ 30 ng/mL. There are other studies also showing inverse relationship between UVB and pancreatic cancer (Kato et al. 1985; Giovannucci et al. 2006; Neale et al. 2009). Interestingly, high insulin and glucose levels have been found to be related to pancreatic cancer positively (Hennig et al. 2004; Stolzenberg-Solomon et al. 2005; Huxley et al. 2005; Michaud et al. 2007). Since vitamin D is able to regulate the synthesis, binding and actions of insulin (Maestro et al. 2000; Maestro et. 2003; Mathieu et al. 2005), there seems to be an inverse relationship between pancreatic cancer incidence and vitamin D status. Due to these contradictory findings, more careful studies should be conducted to investigate the

potential impacts of gene polymorphisms, including VDR, DBP, *CYP27B1*, and *CYP24A1*, on vitamin D status in order to determine whether adequate vitamin D nutrition has a survival and/or a preventive benefit against the pancreatic cancer.

8. Conclusion

Pancreatic cancer is often diagnosed at a late stage with a 5-year survival of merely 1-4%. Its characteristics of early spread and distant metastasis at the time of diagnosis make it a poor candidate for surgical treatment. Moreover, traditional chemotherapy and radiotherapy fail to show significant benefit on survival of PCA patients, and no effective target therapy against PCA is available at the present time. Since clinicians are faced with the dilemma of dealing with advanced PCA, developing new regimens against PCA deserve more attention. Vitamin D, originally discovered for treating rickets a century ago, has been found to go through a series of hydroxylation steps, leading to the synthesis of the active metabolite, $1\alpha,25(\text{OH})_2\text{D}_3$. The active metabolite exerts an array of actions through its binding to VDR, which is found to exist in almost all tissues in humans. Although $1\alpha,25(\text{OH})_2\text{D}_3$ possesses antitumor effects on many cancer cells *in vitro* and *in vivo*, its clinical application is impeded by the lethal side effect of hypercalcemia when administered systemically. To overcome this drawback, thousands of $1\alpha,25(\text{OH})_2\text{D}_3$ analogues have been synthesized, and some of them have much less calcemic activity and/or a more potent antitumor effect. Regarding pancreatic cancer, although several analogues have shown promising antiproliferative effect on cells in culture and animal experiments, they fail to offer any benefits in clinical trials. However, in combination with docetaxel, $1\alpha,25(\text{OH})_2\text{D}_3$ was able to prolong the period of time-to-progression of patients with advanced pancreatic cancer. Recently, two analogues of $1\alpha,25(\text{OH})_2\text{D}_3$, $1,25(\text{OH})_2\text{D}_3$ -3-BE and MART-10, have been shown to exert much greater antiproliferative effect on pancreatic cancer cells *in vitro*. Under the current situation without an effective treatment for the advanced PCA, further investigation of these two analogues in animal models and clinical trials is warranted.

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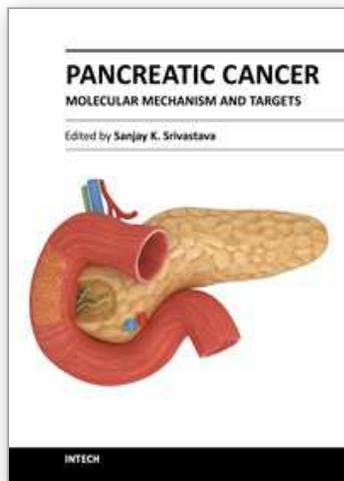
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Pancreatic Cancer - Molecular Mechanism and Targets

Edited by Prof. Sanjay Srivastava

ISBN 978-953-51-0410-0

Hard cover, 432 pages

Publisher InTech

Published online 23, March, 2012

Published in print edition March, 2012

This book provides the reader with an overall understanding of the biology of pancreatic cancer, hereditary, complex signaling pathways and alternative therapies. The book explains nutrigenomics and epigenetics mechanisms such as DNA methylation, which may explain the etiology or progression of pancreatic cancer. Book also summarizes the molecular control of oncogenic pathways such as K-Ras and KLF4. Since pancreatic cancer metastasizes to vital organs resulting in poor prognosis, special emphasis is given to the mechanism of tumor cell invasion and metastasis. Role of nitric oxide and Syk kinase in tumor metastasis is discussed in detail. Prevention strategies for pancreatic cancer are also described. The molecular mechanisms of the anti-cancer effects of curcumin, benzyl isothiocyanate and vitamin D are discussed in detail. Furthermore, this book covers the basic mechanisms of resistance of pancreatic cancer to chemotherapy drugs such as gemcitabine and 5-flourouracil.

How to reference

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Kun-Chun Chiang and Tai C. Chen (2012). Vitamin D for the Prevention and Treatment of Pancreatic Cancer, Pancreatic Cancer - Molecular Mechanism and Targets, Prof. Sanjay Srivastava (Ed.), ISBN: 978-953-51-0410-0, InTech, Available from: <http://www.intechopen.com/books/pancreatic-cancer-molecular-mechanism-and-targets/vitamin-d-in-the-prevention-and-treatment-of-pancreatic-cancer>

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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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