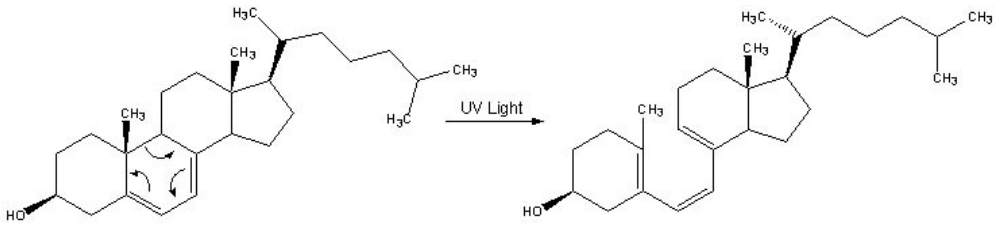
VITAMINA D

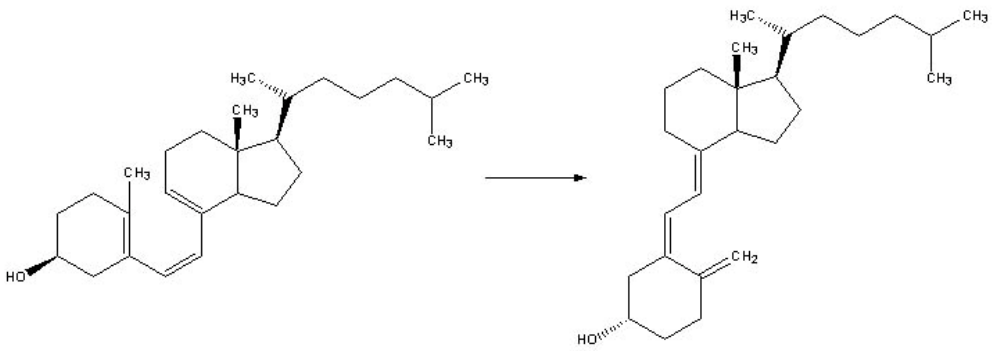
IN

MALATTIE LINFOPROLIFERATIVE

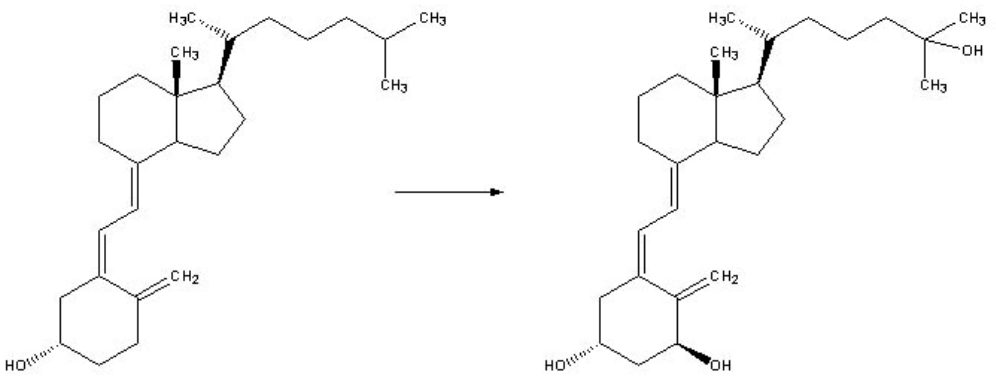
Reazione Deidrocolesterolo → Previtamina D3



Reazione Previtamina D3 → Vitamina D3



Reazione Vitamina D3 → Calcitriolo



Introduzione

La vitamina D è un ormone steroideo che negli esseri umani è sintetizzata nella pelle a partire dal 7-deidrocolesterolo in presenza di luce UV. Essa viene anche assunta da fonti dietetiche. La vitamina D è principalmente metabolizzata nel fegato e successivamente nel rene in 1,25-diidroidrossivitamina D (calcitriolo), il metabolita biologicamente più attivo della vitamina D. Il calcitriolo a sua volta controlla nell'organismo l'omeostasi del calcio e del fosfato (Zittermann 2003; Calvo, Whiting et al. 2005).

La vitamina D ed i suoi analoghi esercitano la loro attività attraverso vie regolative genomiche e non genomiche. La risposta genomica classica è mediata attraverso il recettore della vitamina D (VDR), un membro della superfamiglia dei recettori degli ormoni steroidei (Mangelsdorf, Thummel et al. 1995). Recettori della vitamina D sono stati identificati in oltre 30 tipi di tessuti diversi, tra cui l'intestino, il rene, l'osso, il cervello, lo stomaco, il cuore, il pancreas, la pelle, il colon, l'ovaio, il seno, la prostata e i linfonodi (Berger, Wilson et al. 1988; Holick 2003). Ciò indica un ruolo per la vitamina D nella regolazione della crescita e dello sviluppo normale di molti tipi cellulari, a livello locale.
La vitamina D influenza anche diverse vie di segnale citoplasmatiche mediante fattori regolativi tra cui la protein chinasi C (PKC) e la protein chinasi attivata da mitogeno (MAPK) (Beno, Brady et al. 1995).

Nel 1981 fu dimostrata per la prima volta un'attività antineoplastica della vitamina D; fu riportato che cellule di leucemia mieloide murina possedevano VDR ed il trattamento con vitamina D induceva tali cellule a differenziare terminalmente (Abe, Miyaura et al. 1981). Da allora, l'attività antineoplastica dei ligandi dei VDR è stata dimostrata sia in vitro che in vivo, in molti tipi di neoplasie diverse, tra cui:

- carcinoma del colon (Cross, Huber et al. 1991);
- carcinoma del seno (Colston, Chander et al. 1992);
- carcinoma della vescica (Konety, Lavelle et al. 2001);
- carcinoma del rene (Fujioka, Hasegawa et al. 1998);
- carcinoma del polmone (Higashimoto, Ohata et al. 1996);
- carcinoma del pancreas (Zugmaier, Jager et al. 1996);
- carcinoma della prostata (Peehl, Skowronski et al. 1994);
- carcinoma a cellule squamose (Hershberger, Modzelewski et al. 1999);
- sarcomi dei tessuti molli (Shabahang, Buffan et al. 1996);
- osteosarcomi (Hara, Kusuzaki et al. 2001);
- neuroblastoma (Celli, Treves et al. 1999);
- glioma (Naveilhan, Berger et al. 1994);

- melanoma (Colston, Colston et al. 1981);
- leucemia (Takahashi, Nakamura et al. 1997);
- linfoma (Consolini, Pala et al. 2001);
- mieloma (Puthier, Bataille et al. 1996);

La vitamina D ed i suoi analoghi esercitano la loro attività antineoplastica mediante diversi meccanismi:

- Inibizione della proliferazione da parte dei ligandi dei VDR è stata dimostrata in vari tipi di cellule neoplastiche. La vitamina D e i suoi analoghi inducono arresto in fase G1 del ciclo cellulare in numerose linee cellulari tumorali, tra cui cellule leucemiche, cellule di carcinoma (Guyton, Kensler et al. 2003; Beer and Myrthue 2004).
- L'inibizione della proliferazione indotta dai ligandi dei VDR è spesso associata ad induzione del differenziamento terminale, come dimostrato in cellule leucemiche e di carcinoma (Guyton, Kensler et al. 2003; Beer and Myrthue 2004).
- È stato dimostrato che la vitamina D è in grado di indurre il processo di apoptosi in diversi modelli tumorali, tra cui carcinomi del colon, del seno, della prostata così come nel mieloma e nella leucemia linfocitica cronica a cellule-B (Guyton, Kensler et al. 2003; Beer and Myrthue 2004).
- La vitamina D può anche influenzare il processo di invasione tumorale e metastasi. Saggi in vitro mostrano che la vitamina D è capace di inibire l'invasività di cellule di carcinoma del polmone, del seno e della prostata. Inibizione, in vivo, di metastasi tumorali è stata anche dimostrata in diversi modelli di tumori di roditori, tra cui cancro della vescica, della prostata e melanoma (Guyton, Kensler et al. 2003; Beer and Myrthue 2004).
- Inibizione dell'angiogenesi può anche contribuire all'attività anti-metastatica della vitamina D. In vitro, la vitamina D inibisce la proliferazione di cellule endoteliali derivate da tumore ed inibisce alcuni processi angiogenetici indotti dal fattore di crescita endoteliale vascolare (VEGF) (Bernardi, Johnson et al. 2002). Inoltre, è stato mostrato che, in vivo nei topi, la vitamina D inibisce l'angiogenesi indotta da tumore (Majewski, Skopinska et al. 1996).

Il riconoscimento degli effetti antineoplastici della vitamina D ha indotto a valutare possibili effetti sinergici della vitamina D stessa con altre molecole, con attività anti-tumorale. È stato mostrato che:

- I ligandi dei VDR potenziano l'attività anti-tumorale di diversi chemioterapici, come il cisplatino, i taxani ed il tamoxifen (Abe-Hashimoto, Kikuchi et al. 1993; Moffatt, Johannes et al. 1999; Hershberger, Yu et al. 2001)
- Il dexametasone potenzia gli effetti antitumorali della vitamina D, sia in vitro che in vivo (Bernardi, Trump et al. 2001).

- La vitamina D ed i retinoidi in combinazione hanno un effetto sinergico su processi come inibizione della crescita ed angiogenesi (Makishima, Kanatani et al. 1996; Guzey, Sattler et al. 1998).

Vitamina D in malattie linfoproliferative

La vitamina D induce inibizione della proliferazione e differenziamento terminale in diverse linee cellulari leucemiche e in blasti leucemici di pazienti. Questo effetto è mediato attraverso il recettore della vitamina D3, che è espresso in cellule del sistema emopoietico, sia normali che maligne (Kizaki, Norman et al. 1991; Manolagas, Yu et al. 1994).

La vitamina D induce una significativa inibizione della crescita di progenitori cellulari linfoidi normali, sia di tipo B che di tipo T. La vitamina D inibisce in modo significativo anche la crescita di cellule progenitrici linfoidi maligne di tipo B (Consolini, Pala et al. 2001).

In modelli murini di linfoma è stato dimostrato che la vitamina D inibisce la progressione delle cellule di linfoma attraverso diversi meccanismi. Topi trapiantati con cellule di linfoma trattati con vitamin D mostrano un aumento della sopravvivenza rispetto a quelli non trattati con vitamin D (Sardar, Chatterjee et al. 1996). Inoltre, il trattamento con vitamin D induce un'elevata attività di glutatione S-transferasi citosolica (Sardar, Chatterjee et al. 1996). È stato anche riportato che in linfomi murini trapiantabili la vitamina D ha proprietà anticlastogeniche, cioè limita la frequenza di aberrazioni cromosomiche e lo scambio di cromatidi fratelli, contrastando così lo sviluppo del processo tumorale (Sarkar, Saha et al. 2000).

Un recente studio epidemiologico ha mostrato, contrariamente alle aspettative, un'associazione inversa tra esposizione al sole ed incidenza di linfoma non-Hodgkin (Hughes, Armstrong et al. 2004). Tale associazione sembra più forte in donne e bambini. Le sempre più numerose evidenze che la vitamina D protegge contro il cancro rendono la sintesi di vitamina D, mediata da luce UV, un meccanismo plausibile per cui l'esposizione al sole può proteggere contro lo sviluppo di linfoma non-Hodgkin (Hughes, Armstrong et al. 2004).

Sono stati riportati alcuni casi clinici di pazienti con malattie linfoproliferative trattati con ligandi del recettore della vitamina D.
La remissione di linfoma cutaneo a cellule T è stata ottenuta con una combinazione di calcitriolo (1,25-diidroidrossivitamina D) ed acitretin (French, Ramelet et al. 1994).
Un altro paziente con leucemia cronica a cellule-B ha risposto al trattamento con Alfarol (1-alpha[OH] D3) (Hashimoto, Takeuchi et al. 1989).
Infine l'alfacalcidol (1-alfa-idrossicolecalciferolo) ha mostrato attività antitumorale in pazienti con linfomi non-Hodgkin a basso grado (Cunningham, Gilchrist et al. 1985).

BIBLIOGRAFIA

Abe-Hashimoto, J., T. Kikuchi, et al. (1993). "Antitumor effect of 22-oxa-calcitriol, a noncalcemic analogue of calcitriol, in athymic mice implanted with human breast carcinoma and its synergism with tamoxifen." Cancer Res **53**(11): 2534-7.

Abe, E., C. Miyaura, et al. (1981). "Differentiation of mouse myeloid leukemia cells induced by 1 alpha,25-dihydroxyvitamin D3." Proc Natl Acad Sci U S A **78**(8): 4990-4.

Beer, T. M. and A. Myrthue (2004). "Calcitriol in cancer treatment: from the lab to the clinic." Mol Cancer Ther **3**(3): 373-81.

Beno, D. W., L. M. Brady, et al. (1995). "Protein kinase C and mitogen-activated protein kinase are required for 1,25-dihydroxyvitamin D3-stimulated Egr induction." J Biol Chem **270**(8): 3642-7.

Berger, U., P. Wilson, et al. (1988). "Immunocytochemical detection of 1,25-dihydroxyvitamin D receptors in normal human tissues." J Clin Endocrinol Metab **67**(3): 607-13.

Bernardi, R. J., C. S. Johnson, et al. (2002). "Antiproliferative effects of 1alpha,25-dihydroxyvitamin D(3) and vitamin D analogs on tumor-derived endothelial cells." Endocrinology **143**(7): 2508-14.

Bernardi, R. J., D. L. Trump, et al. (2001). "Combination of 1alpha,25-dihydroxyvitamin D(3) with dexamethasone enhances cell cycle arrest and apoptosis: role of nuclear receptor cross-talk and Erk/Akt signaling." Clin Cancer Res **7**(12): 4164-73.

Calvo, M. S., S. J. Whiting, et al. (2005). "Vitamin D intake: a global perspective of current status." J Nutr **135**(2): 310-6.

Celli, A., C. Treves, et al. (1999). "Vitamin D receptor in SH-SY5Y human neuroblastoma cells and effect of 1,25-dihydroxyvitamin D3 on cellular proliferation." Neurochem Int **34**(2): 117-24.

Colston, K., M. J. Colston, et al. (1981). "1,25-dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture." Endocrinology **108**(3): 1083-6.

Colston, K. W., S. K. Chander, et al. (1992). "Effects of synthetic vitamin D analogues on breast cancer cell proliferation in vivo and in vitro." Biochem Pharmacol **44**(4): 693-702.

Consolini, R., S. Pala, et al. (2001). "Effects of vitamin D on the growth of normal and malignant B-cell progenitors." Clin Exp Immunol **126**(2): 214-9.

Cross, H. S., C. Huber, et al. (1991). "Antiproliferative effect of 1,25-dihydroxyvitamin D3 and its analogs on human colon adenocarcinoma cells (CaCo-2): influence of extracellular calcium." Biochem Biophys Res Commun **179**(1): 57-62.

Cunningham, D., N. L. Gilchrist, et al. (1985). "Alfacalcidol as a modulator of growth of low grade non-Hodgkin's lymphomas." Br Med J (Clin Res Ed) **291**(6503): 1153-5.

French, L. E., A. A. Ramelet, et al. (1994). "Remission of cutaneous T-cell lymphoma with combined calcitriol and acitretin." Lancet **344**(8923): 686-7.

Fujioka, T., M. Hasegawa, et al. (1998). "Inhibition of tumor growth and angiogenesis by vitamin D3 agents in murine renal cell carcinoma." J Urol **160**(1): 247-51.

Guyton, K. Z., T. W. Kensler, et al. (2003). "Vitamin D and vitamin D analogs as cancer chemopreventive agents." Nutr Rev **61**(7): 227-38.

Guzey, M., C. Sattler, et al. (1998). "Combinational effects of vitamin D3 and retinoic acid (all trans and 9 cis) on proliferation, differentiation, and programmed cell death in two small cell lung carcinoma cell lines." Biochem Biophys Res Commun **249**(3): 735-44.

Hara, K., K. Kusuzaki, et al. (2001). "Oral administration of 1 alpha hydroxyvitamin D3 inhibits tumor growth and metastasis of a murine osteosarcoma model." Anticancer Res **21**(1A): 321-4.

Hashimoto, E., H. Takeuchi, et al. (1989). "[1 alpha(OH) D3 (Alfarol) is effective for the treatment of chronic B cell leukemia: a case report]." Rinsho Ketsueki **30**(10): 1876-80.

Hershberger, P. A., R. A. Modzelewski, et al. (1999). "1,25-Dihydroxycholecalciferol (1,25-D3) inhibits the growth of squamous cell carcinoma and down-modulates p21(Waf1/Cip1) in vitro and in vivo." Cancer Res **59**(11): 2644-9.

Hershberger, P. A., W. D. Yu, et al. (2001). "Calcitriol (1,25-dihydroxycholecalciferol) enhances paclitaxel antitumor activity in vitro and in vivo and accelerates paclitaxel-induced apoptosis." Clin Cancer Res **7**(4): 1043-51.

Higashimoto, Y., M. Ohata, et al. (1996). "1 alpha, 25-dihydroxyvitamin D3 and all-trans-retinoic acid inhibit the growth of a lung cancer cell line." Anticancer Res **16**(5A): 2653-9.

Holick, M. F. (2003). "Vitamin D: A millenium perspective." J Cell Biochem **88**(2): 296-307.

Hughes, A. M., B. K. Armstrong, et al. (2004). "Sun exposure may protect against non-Hodgkin lymphoma: a case-control study." Int J Cancer **112**(5): 865-71.

Kizaki, M., A. W. Norman, et al. (1991). "1,25-Dihydroxyvitamin D3 receptor RNA: expression in hematopoietic cells." Blood **77**(6): 1238-47.

Konety, B. R., J. P. Lavelle, et al. (2001). "Effects of vitamin D (calcitriol) on transitional cell carcinoma of the bladder in vitro and in vivo." J Urol **165**(1): 253-8.

Majewski, S., M. Skopinska, et al. (1996). "Vitamin D3 is a potent inhibitor of tumor cell-induced angiogenesis." J Investig Dermatol Symp Proc **1**(1): 97-101.

Makishima, M., Y. Kanatani, et al. (1996). "Enhancement of activity of 1alpha, 25-dihydroxyvitamin D3 for growth inhibition and differentiation induction of human myelomonocytic leukemia cells by tretinoin tocoferil, an alpha-tocopherol ester of all-trans retinoic acid." Blood **87**(8): 3384-94.

Mangelsdorf, D. J., C. Thummel, et al. (1995). "The nuclear receptor superfamily: the second decade." Cell **83**(6): 835-9.

Manolagas, S. C., X. P. Yu, et al. (1994). "Vitamin D and the hematolymphopoietic tissue: a 1994 update." Semin Nephrol **14**(2): 129-43.

Moffatt, K. A., W. U. Johannes, et al. (1999). "1Alpha,25dihydroxyvitamin D3 and platinum drugs act synergistically to inhibit the growth of prostate cancer cell lines." Clin Cancer Res **5**(3): 695-703.

Naveilhan, P., F. Berger, et al. (1994). "Induction of glioma cell death by 1,25(OH)2 vitamin D3: towards an endocrine therapy of brain tumors?" J Neurosci Res **37**(2): 271-7.

Peehl, D. M., R. J. Skowronski, et al. (1994). "Antiproliferative effects of 1,25-dihydroxyvitamin D3 on primary cultures of human prostatic cells." Cancer Res **54**(3): 805-10.

Puthier, D., R. Bataille, et al. (1996). "Myeloma cell growth arrest, apoptosis, and interleukin-6 receptor modulation induced by EB1089, a vitamin D3 derivative, alone or in association with dexamethasone." Blood **88**(12): 4659-66.

Sardar, S., M. Chatterjee, et al. (1996). "Role of vitamin D3 on the activity patterns of hepatic drug metabolizing enzymes in transplantable murine lymphoma." Cancer Invest **14**(4): 328-34.

Sarkar, A., B. K. Saha, et al. (2000). "Anticlastogenic potential of 1alpha,25-dihydroxyvitamin D3 in murine lymphoma." Cancer Lett **150**(1): 1-13.

Shabahang, M., A. E. Buffan, et al. (1996). "The effect of 1, 25-dihydroxyvitamin D3 on the growth of soft-tissue sarcoma cells as mediated by the vitamin D receptor." Ann Surg Oncol **3**(2): 144-9.

Takahashi, T., K. Nakamura, et al. (1997). "Differentiation of myeloid cells and 1,25-dihydroxyvitamin D3." Leuk Lymphoma **27**(1-2): 25-33.

Zittermann, A. (2003). "Vitamin D in preventive medicine: are we ignoring the evidence?" Br J Nutr **89**(5): 552-72.

Zugmaier, G., R. Jager, et al. (1996). "Growth-inhibitory effects of vitamin D analogues and retinoids on human pancreatic cancer cells." Br J Cancer **73**(11): 1341-6.

Clin Cancer Res. 2001 Apr;7(4):1043-51.

Calcitriol (1,25-dihydroxycholecalciferol) enhances paclitaxel antitumor activity in vitro and in vivo and accelerates paclitaxel-induced apoptosis.

Hershberger PA, Yu WD, Modzelewski RA, Rueger RM, Johnson CS, Trump DL.

We demonstrated that calcitriol has antiproliferative activity in squamous cell carcinoma and prostatic adenocarcinoma and enhances the antitumor activity of platinum-based agents. In this study, we examined whether calcitriol also increases paclitaxel cytotoxicity. The effect of treatment on growth of the murine squamous cell carcinoma (SCCVII/SF) and human prostatic adenocarcinoma (PC-3) was determined by clonogenic assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, and monitoring tumor growth. Treatment of SCC or PC-3 cells in vitro with calcitriol prior to paclitaxel significantly reduced clonogenic survival compared with either agent alone. Median-dose effect analysis revealed that calcitriol and paclitaxel interact synergistically. Treatment of SCC or PC-3 tumor-bearing mice with calcitriol prior to paclitaxel resulted in substantially greater growth inhibition than was achieved with either agent alone, supporting the combined use of calcitriol and paclitaxel in the treatment of solid tumors. To explore the molecular basis for the enhanced antitumor activity of this combination, the effect of treatment on p21(Waf-1) (p21), Bcl-2, and poly(ADP-ribose) polymerase expression was evaluated in PC-3. A 72-h pretreatment with calcitriol reduced p21 expression and increased paclitaxel cytotoxicity (measured after 24 h) without evidence of apoptosis [poly(ADP-ribose) polymerase cleavage]. After 48 h, paclitaxel induced apoptosis, the extent of which was increased similarly by pretreatment or concurrent treatment with calcitriol. We therefore propose a model for calcitriol enhancement of paclitaxel cytotoxicity in which the "early" (24 h) effects are schedule dependent and not attributed to enhancement of paclitaxel-induced apoptosis. In contrast, the "delayed" (48-h) enhancement of paclitaxel activity by calcitriol is schedule independent and associated with acceleration of apoptosis.

Cancer Res. 1999 Jun 1;59(11):2644-9.

1,25-Dihydroxycholecalciferol (1,25-D3) inhibits the growth of squamous cell carcinoma and down-modulates p21(Waf1/Cip1) in vitro and in vivo.

Hershberger PA, Modzelewski RA, Shurin ZR, Rueger RM, Trump DL, Johnson CS.

1,25-Dihydroxycholecalciferol (1,25-D3) has significant antitumor effects in the murine squamous cell carcinoma (SCC) tumor model in vitro and in vivo. We investigated the basis for this antiproliferative activity and found that, in vitro, 1,25-D3 administration is associated with altered expression of cell cycle regulatory proteins, treatment results in retinoblastoma dephosphorylation, decreased expression of p21(Waf1/Cip1) (p21) mRNA and protein, and increased expression of p27Kip1 (p27) mRNA and protein. Dexamethasone, which acts synergistically with 1,25-D3 to inhibit SCC proliferation, enhanced 1,25-D3-induced down-modulation of p21 without affecting the ability of 1,25-D3 to increase p27 expression. 1,25-D3 did not induce cleavage of poly(ADP-ribose) polymerase. These in vitro data suggest that 1,25-D3 exerts antitumor activity in SCC by perturbing cell cycle progression rather than by inducing apoptosis. In vivo, a 1,25-D3 treatment regimen that results in a decrease in SCC tumor volume is associated with a statistically significant decrease in intratumoral p21 expression. p21 expression is not changed in tumors isolated from control animals or animals treated with a nontherapeutic dose of 1,25-D3. Intratumoral p27 levels were not modulated by 1,25-D3 treatment. Thus, both in vitro and in vivo, 1,25-D3-mediated growth inhibition is associated with p21 down-modulation.

Anticancer Res. 1996 Sep-Oct;16(5A):2653-9.

1 alpha, 25-dihydroxyvitamin D3 and all-trans-retinoic acid inhibit the growth of a lung cancer cell line.

Higashimoto Y, Ohata M, Nishio K, Iwamoto Y, Fujimoto H, Uetani K, Suruda T, Nakamura Y, Funasako M, Saijo N.

The secosteroid 1 alpha, 25-dihydroxyvitamin D3 (calcitriol) and retinoic acid are the major biologically active metabolites of vitamins D and A, respectively. Their antitumor activity has been observed in several cancer cells in vitro apart from lung cancer cells. The purpose of this study was to examine the possible effects of the agents on lung cancer cell lines. The responses of five lung cancer cell lines to calcitriol or all-transretinoic acid (RA) were assessed by a colorimetric MTT assay. Calcitriol inhibited growth in one of the tested cell lines, i.e. EBC-1 squamous cell carcinoma, dose dependently. RA also exhibited the same effect in EBC-1 cells. However neither agent affected the growth of other lung cancer cell lines. Subsequently we examined the mRNA expression of vitamin D receptor (VDR) and retinoic acid receptor (RAR alpha) in these lung cancer cells by quantitative RT-PCR. EBC-1 cells expressed high levels of mRNA for both VDR and RAR alpha, while other cell lines expressed much lower mRNA levels for the receptors. These data suggest that the growth inhibitory effects of the vitamins are associated with mRNA expression for VDR and RAR alpha.

J Cell Biochem. 2003 Feb 1;88(2):296-307.

Vitamin D: A millenium perspective.

Holick MF.

Vitamin D is one of the oldest hormones that have been made in the earliest life forms for over 750 million years. Phytoplankton, zooplankton, and most plants and animals that are exposed to sunlight have the capacity to make vitamin D. Vitamin D is critically important for the development, growth, and maintenance of a healthy skeleton from birth until death. The major function of vitamin D is to maintain calcium homeostasis. It accomplishes this by increasing the efficiency of the intestine to absorb dietary calcium. When there is inadequate calcium in the diet to satisfy the body's calcium requirement, vitamin D communicates to the osteoblasts that signal osteoclast precursors to mature and dissolve the calcium stored in the bone. Vitamin D is metabolized in the liver and then in the kidney to 1,25-dihydroxyvitamin D [1,25(OH)(2)D]. 1,25(OH)(2)D receptors (VDR) are present not only in the intestine and bone, but in a wide variety of other tissues, including the brain, heart, stomach, pancreas, activated T and B lymphocytes, skin, gonads, etc. 1,25(OH)(2)D is one of the most potent substances to inhibit proliferation of both normal and hyperproliferative cells and induce them to mature. It is also recognized that a wide variety of tissues, including colon, prostate, breast, and skin have the enzymatic machinery to produce 1,25(OH)(2)D. 1,25(OH)(2)D and its analogs have been developed for treating the hyperproliferative disease psoriasis. Vitamin D deficiency is a major unrecognized health problem. Not only does it cause rickets in children, osteomalacia and osteoporosis in adults, but may have long lasting effects. Chronic vitamin D deficiency may have serious adverse consequences, including increased risk of hypertension, multiple sclerosis, cancers of the colon, prostate, breast, and ovary, and type 1 diabetes. There needs to be a better appreciation of the importance of vitamin D for overall health and well being.

Int J Cancer. 2004 Dec 10;112(5):865-71.

Sun exposure may protect against non-Hodgkin lymphoma: a case-control study.

Hughes AM, Armstrong BK, Vajdic CM, Turner J, Grulich AE, Fritschi L, Milliken S, Kaldor J, Benke G, Kricker A.

Ultraviolet radiation is a hypothesised risk factor for non-Hodgkin lymphoma (NHL) but no epidemiological study has examined this association using direct measures of sun exposure in individuals. Adults aged 20-74 years living in NSW and ACT, Australia, were the study population. Cases (704 of 829 invited to take part, 85%) were diagnosed January 2000 to August 2001. Controls (694 of 1,136 invited to take part, 61%) were randomly selected from state electoral rolls and frequency-matched to cases by age, sex and state of residence. A self-administered questionnaire and telephone interview measured outdoor hours on working and nonworking days and vacations at 10, 20, 30, 40, 50 and 60 years of age. Logistic regression models of NHL and sun exposure contained the 3 matching variables, ethnicity and sun sensitivity measures as covariates. Contrary to expectations, risk of NHL fell with increasing reported sun exposure hours. Relative to 1.0 for the lowest quarter of total sun exposure hours, the odds ratios (ORs) for successively higher quarters were 0.72 (95% CI 0.53-0.98), 0.66 (0.48-0.91) and 0.65 (0.46-0.91) (p(trend)=0.01). The association of sun exposure on nonworking days with NHL was stronger; OR for highest quarter 0.47 (0.34-0.66) (p(trend)=0.0001). Risk also fell with sun exposure on vacations; OR for highest quarter 0.60 (0.43-0.85) (p(trend)=0.003). These associations appeared strongest in women and in childhood. There was little evident trend in risk with exposure on working day. Our results provide strong statistical evidence for an inverse association between sun exposure and NHL. Increasing evidence that vitamin D may protect against cancer makes UV-mediated synthesis of vitamin D a plausible mechanism whereby sun exposure might protect against NHL.

Blood. 1991 Mar 15;77(6):1238-47.

1,25-Dihydroxyvitamin D3 receptor RNA: expression in hematopoietic cells.

Kizaki M, Norman AW, Bishop JE, Lin CW, Karmakar A, Koeffler HP.

1,25-Dihydroxyvitamin D3 [1,25(OH)2D3] induces differentiation and inhibits proliferation of myeloid leukemic cells from various lines and patients; these effects are probably mediated through the 1,25(OH)2D3 receptor. Little is known of expression of 1,25(OH)2D3 receptor RNA in hematopoietic cells. We examined the expression and modulation of expression of 1,25(OH)2D3 receptor RNA in various proliferating and nonproliferating hematopoietic cells. Constitutive expression of 1,25(OH)2D3 receptor RNA was detected in various kinds of hematopoietic cells, including macrophages and activated T lymphocytes, as well as in cell lines KG-1 (myeloblasts), HL-60 (promyelocytes), ML-3 (myelomonoblasts), U937, THP-1 (monoblasts), K562 (erythroblasts), and S-LB1 (HTLV-1-transfected T lymphocytes). Receptor transcripts were 4.6 kilobases (kb), and no variant sizes were observed. All cell lines examined in this group also expressed 1,25(OH)2D3 receptors. Most B lymphocyte lines expressed negligible levels of 1,25(OH)2D3 receptor RNA and protein; however; analysis of a lymphoid/myeloid somatic hybrid suggested that suppression of expression of 1,25(OH)2D3 receptor RNA in B lymphocytes may be a dominant characteristic. HL-60 cells were cultured with 10(-7) mol/L 1,25(OH)2D3 for 24 to 72 hours, and levels of expression of 1,25(OH)2D3 receptor and its RNA were examined. Levels of RNA coding for the receptor were not modulated by exposure to high levels of ligand. Levels of occupied 1,25(OH)2D3 receptor protein increased in these HL-60 cells; but the total number of 1,25(OH)2D3 receptors decreased about 50% at 24 hours and returned toward normal at 72 hours. Steady-state levels of 1,25(OH)2D3 receptor RNA were not affected by terminal differentiation of HL-60 toward either granulocytes or macrophages. Nondividing macrophages from normal individuals also expressed 1,25(OH)2D3 receptor RNA. In contrast, nondividing peripheral blood lymphocytes from normal individuals did not express 1,25(OH)2D3 receptor RNA; with stimulation of proliferation of these cells, accumulation of 1,25(OH)2D3 receptor RNA increased markedly. Half-life (t1/2) of 1,25(OH)2D3 receptor RNA in T lymphocytes was short (1 hour) as determined by measuring decay of the message after addition of actinomycin D. Consistent with this short t1/2, accumulation of 1,25(OH)2D3 receptor RNA increased in cells as their protein synthesis was inhibited. Further studies are required to understand the physiologic role of 1,25(OH)2D3 receptors in myeloid cells and proliferating T lymphocytes.

J Urol. 2001 Jan;165(1):253-8.

Effects of vitamin D (calcitriol) on transitional cell carcinoma of the bladder in vitro and in vivo.

Konety BR, Lavelle JP, Pirtskalaishvili G, Dhir R, Meyers SA, Nguyen TS, Hershberger P, Shurin MR, Johnson CS, Trump DL, Zeidel ML, Getzenberg RH.

PURPOSE: Vitamin D (calcitriol) has significant antiproliferative effects on various tumor cells in vitro and in vivo. In the clinical situation a major impediment to systemic administration of calcitriol is the side effect of hypercalcemia. To test the potential usefulness of calcitriol for bladder cancer treatment, we studied the antiproliferative effect of vitamin D on 2 human bladder cancer cell lines, 253j and T-24, in vitro. We also examined the in vivo effects of calcitriol in an animal model of bladder cancer using intravesical administration to avoid the toxicity of systemic calcitriol therapy. MATERIALS AND METHODS: The presence of vitamin D receptors in normal and neoplastic human bladder tissue, and tumor cells T-24 and 253j was determined by immunoblot analysis. Tumor cell proliferation in the presence or absence of calcitriol was determined using a crystal violet assay. Calcitriol induced apoptosis was determined by morphology, polyadenosine diphosphate ribose polymerase cleavage and annexin V binding. In vivo studies were performed by weekly intravesical instillation of calcitriol in female Fischer 344 rats after induction of tumors by N-methyl nitrosourea. Calcitriol administration was started 3 weeks after tumor induction for 7 doses at weekly intervals. RESULTS: Normal and neoplastic human bladder tissue, and the cell lines expressed vitamin D receptors. In the 253j and T-24 cell lines proliferation was significantly inhibited by calcitriol. Progressive cleavage of full length polyadenosine diphosphate ribose polymerase was observed in calcitriol treated cells starting as early as 4 hours after exposure. Similar changes were not observed in the control cells treated with vehicle (ethanol) alone. After 24 hours of treatment with calcitriol 45.8% of 253j cells bound annexin compared to 16.5% of control cells (chi-square $p < 0.001$). Of the control animals 66% developed bladder tumors and 55% of the animals treated with calcitriol early (3 weeks) after tumor induction developed bladder tumors. Almost all of the tumors that developed in the calcitriol group were unifocal, and only 20% were invasive compared to 50% of those in the control animals. CONCLUSIONS: These results demonstrate that calcitriol inhibits proliferation and induces apoptosis in human bladder tumor cells in vitro, and may have therapeutic potential in bladder cancer. In vivo studies using an N-methylnitrosourea induced model of bladder cancer demonstrate that early institution of intravesical calcitriol therapy after carcinogen exposure results in fewer tumors, which are also less likely to be multifocal, high grade

or invasive. With our protocol a short course of intravesical calcitriol administration did not result in any significant toxicity.

J Investig Dermatol Symp Proc. 1996 Apr;1(1):97-101.

Vitamin D3 is a potent inhibitor of tumor cell-induced angiogenesis.

Majewski S, Skopinska M, Marczak M, Szmurlo A, Bollag W, Jablonska S.

Vitamin D3 derivative 1,25-dihydroxyvitamin D3 (1,25[OH]2D3) exerts various biological effects in cells that possess vitamin D3 receptor (VDR), including enhancement of cell differentiation and inhibition of cell proliferation. These activities of 1,25(OH)2D3 might be responsible for its anti-neoplastic effects, as shown in various experimental systems. The aim of this study was to compare the anti-angiogenic activity of 1,25(OH)2D3, retinoids, and interleukin-12 (IL-12) in an experimental tumor cell-induced angiogenesis assay in mice. Tumor cell-induced angiogenesis assay was performed in x-ray immunosuppressed BALB/c mice by intradermal injections of human tumor cell lines of different origin. The injections resulted within 3 d in a local formation of new blood vessels, and the intensity of angiogenesis correlated with the number of injected cells. Systemic treatment of the mouse recipients with 1,25(OH)2D3 significantly decreased angiogenesis, comparable to the effect of retinoids (all-trans retinoic acid [RA], 9-cis RA and 13-cis RA) and of IL-12. In vitro preincubation of the cells with all compounds (except IL-12) led to the inhibition of their angiogenic capability in vivo. Moreover, combination of 1,25(OH)2D3 and retinoids resulted in a synergistic inhibition of angiogenesis. The results strongly suggest that anti-angiogenic compounds with relatively low toxicity (e.g., 1,25(OH)2D3, retinoids, and IL-12) and their combinations could be beneficial in the treatment of some angiogenesis-associated malignancies.

Blood. 1996 Apr 15;87(8):3384-94.

Enhancement of activity of 1alpha, 25-dihydroxyvitamin D3 for growth inhibition and differentiation induction of human myelomonocytic leukemia cells by tretinoin tocoferil, an alpha-tocopherol ester of all-trans retinoic acid.

Makishima M, Kanatani Y, Yamamoto-Yamaguchi Y, Honma Y.

Tretinoin tocoferil is an alpha-tocopherol ester of all-trans retinoic acid (RA) and safely used in the treatment of skin ulcer. Tretinoin tocoferil inhibited proliferation of human promyelocytic leukemia HL-60 cells and induced granulocytic differentiation of the cells, but less than RA. alpha-Tocopherol did not affect differentiation of HL-60 cells, but at high concentrations enhanced its nitroblue tetrazolium (NBT)-reducing activity and expression of surface antigen CD11b, which are markers of myelomonocytic differentiation induced by RA. Tretinoin tocoferil increased NBT reduction in HL-60 cells treated with RA. It also enhanced the differentiation of HL-60 cells induced by dimethyl sulfoxide, phorbol-12-myristate 13-acetate or 1alpha,25-dihydroxyvitamin D3 (VD3). In combination with a low concentration of VD3, it induced the NBT-reducing activity of human monoblastic U937 cells very effectively. Moreover, it enhanced the differentiation of human myelomonocytic ML-1, THP-1, P39/TSU, and P31/FUJ cells induced by VD3. In combination with VD3, it synergistically inhibited the proliferation of HL-60, U937, ML-1, THP-1, P39/TSU, and P31/FUJ cells and decreased the effective concentration of VD3 to a 10(-10) mol/L level. Because tretinoin tocoferil was reported to induce neither retinoid-related toxicity nor teratogenicity, the therapeutic advantage of the use of it in treatment of myelomonocytic leukemia is suggested.

Semin Nephrol. 1994 Mar;14(2):129-43.

Vitamin D and the hematolymphopoietic tissue: a 1994 update.

Manolagas SC, Yu XP, Girasole G, Bellido T.

Monocytes/macrophages and activated (but not resting) lymphocytes as well as certain subsets of thymocytes express the VDR. This protein is indistinguishable from the classical 50-kDa VDR and is encoded by an mRNA with identical nucleotide sequence to that of the human intestinal VDR. Acting via the VDR, 1,25(OH)2D3 modulates the production of a plethora of monocyte, lymphocyte, and bone marrow stromal cell products, including several interleukins and other cytokines, as well as various oncogenes and transcription factors. However, these hormonal effects vary depending on the signals used to activate blood mononuclear cells; moreover, each of the effects of the hormone can be either attenuated, abolished, or even reversed from negative to positive in the presence of phorbol esters. Lymphocytes also express a previously unrecognized 80-kDa cytosolic protein that shares immunologic cross-reactivity with the VDR. This protein is induced on activation and is downregulated by 1,25(OH)2D3, whereas the VDR is upregulated by 1,25(OH)2D3. In contrast to the signal-dependent effects of the hormone on cytokine production and lymphocyte proliferation, the effects of 1,25(OH)2D3 on the 80-kDa protein and VDR are independent of the activation signals. This apparent mechanistic distinction raises the possibility that the signal-independent effects of 1,25(OH)2D3 on the 80-kDa protein and the VDR might be due to direct interactions of the 1,25(OH)2D3-VDR complex with specific response elements (negative and positive VDREs, respectively) on these two genes; as opposed to the signal-dependent effects that might be due to influences of the 1,25(OH)2D3-VDR complex on other transcription factors that are generated in response to the different activation stimuli. Consistent with the second part of this contention, we have recently found that 1,25(OH)2D3 regulates the 50-kDa DNA binding subunit of the pleiotropic transcription factor NF-kappa B and the 105-kDa precursor of this subunit; as well as other members of the rel-related family of proteins, including v-rel and its normal cellular homolog c-rel, in activated normal human lymphocytes. Besides its influence on immune cell products, 1,25(OH)2D3 is a potent agent for the differentiation of cells of the myeloid lineage. In addition, 1,25(OH)2D3 stimulates the fusion and differentiation of hematopoietic progenitors into osteoclasts, an effect which accounts for the potent role of the hormone in bone resorption.(ABSTRACT TRUNCATED AT 400 WORDS).

Clin Cancer Res. 1999 Mar;5(3):695-703.

1Alpha,25dihydroxyvitamin D3 and platinum drugs act synergistically to inhibit the growth of prostate cancer cell lines.

Moffatt KA, Johannes WU, Miller GJ.

The majority of men who die from prostate cancer (PC) have hormone-refractory disease. To date, chemotherapeutic agents have had little or no impact on the survival of such patients. To explore a new approach for the treatment of hormone-refractory PC, we examined the combination effects of cis- or carboplatin with vitamin D. 1alpha,25-Dihydroxyvitamin D3 (1alpha,25(OH)2D3) and its synthetic analogue, Ro 25-6760, have an antiproliferative effect on some prostate cancer cell lines. Consequently, the growth-inhibitory effects of the drugs were measured, both singularly and in combination with cis- or carboplatin, on PC cells. Our results show that although each of the drugs alone displayed antiproliferative activity, the growth inhibition of PC cells was further enhanced by the combination of 1alpha,25(OH)2D3 or Ro 25-6760 and either platinum agent. The greatest enhancement of inhibition occurred using smaller concentrations of the platinum compound in combination with higher concentrations of 1alpha,25(OH)2D3. Isobologram analysis revealed that 1alpha,25(OH)2D3 and platinum acted in a synergistic manner to inhibit the growth of PC cells. Our findings suggest that there is potential clinical value in combining 1alpha,25(OH)2D3 with platinum compounds for the treatment of advanced-stage human PC.

J Neurosci Res. 1994 Feb 1;37(2):271-7.

Induction of glioma cell death by 1,25(OH)2 vitamin D3: towards an endocrine therapy of brain tumors?

Naveilhan P, Berger F, Haddad K, Barbot N, Benabid AL, Brachet P, Wion D.

The secosteroid 1,25-dihydroxyvitamin D3 (1,25 (OH)2D3) is the major biologically active metabolite of vitamin D. Antitumor activity of this hormone has been observed on several cell lines and on breast cancer in vivo. The purpose of this in vitro study was to determine the possible effect of 1,25(OH)2D3 on glioma cells. Two glioma cell lines from rat (C6) or human (GHD) origin were cultured in the presence of 1,25(OH)2D3. The sensitivity of these cells to 1,25 (OH)2D3 was assessed with a colorimetric MTT assay. A cytotoxic effect of 1,25(OH)2D3 was detected at concentrations around 10(-8) M. A lag period of 3 days was required between the onset of the treatment and the observation of the effects. However, the continuous presence of 1,25(OH)2D3 is not required since cell death occurred even when C6 cells were challenged for 24 hr with 1,25(OH)2D3 and then cultured in the absence of the hormone. In addition, 1,25(OH)2D3 regulates the expression of its own receptors in C6 glioma. These results provide to our knowledge the first evidence for a cytotoxic effect of 1,25(OH)2D3 on rat and human glioma cells and could offer both an experimental model to study a programmed cell death in a brain-derived cell line and a new strategy for the inhibition of glioma growth in vivo.

Cancer Res. 1994 Feb 1;54(3):805-10.

Antiproliferative effects of 1,25-dihydroxyvitamin D3 on primary cultures of human prostatic cells.

Peehl DM, Skowronski RJ, Leung GK, Wong ST, Stamey TA, Feldman D.

Cultures of adult human prostatic epithelial and fibroblastic cells were established from normal, benign hyperplastic, and malignant tissues. Vitamin D receptors were detected by ligand binding of [3H]1,25-dihydroxyvitamin D3 [1,25(OH)2D3] in cytosolic extracts prepared from all types of cell cultures as well as from fresh prostatic tissues. Vitamin D receptor transcripts were demonstrated by Northern blot analysis. 1,25-(OH)2D3 inhibited the growth of epithelial cells with half-maximal inhibition at approximately 1 nM. The growth of fibroblasts was also inhibited by 1,25(OH)2D3 but to a lesser extent. This is consistent with the apparently lower level of vitamin D receptors in fibroblasts compared to epithelial cells determined by ligand binding and Northern analysis of RNA transcripts. The growth inhibition of epithelial cells by 1,25(OH)2D3 was irreversible even after a short 2-h exposure, but morphology and keratin expression were not appreciably altered by long-term exposure to the hormone. A physiological role for 1,25(OH)2D3 in the prostate is postulated, and the inhibitory effect of 1,25(OH)2D3 on cancer-derived prostate cells may provide a basis for new preventive or therapeutic strategies.

Blood. 1996 Dec 15;88(12):4659-66.

Myeloma cell growth arrest, apoptosis, and interleukin-6 receptor modulation induced by EB1089, a vitamin D3 derivative, alone or in association with dexamethasone.

Puthier D, Bataille R, Barille S, Mellerin MP, Harousseau JL, Ponzio A, Robillard N, Wijdenes J, Amiot M.

We have previously shown that malignant plasma cells expressed the specific receptor for 1,25-dihydroxyvitamin D3 and that this derivative could significantly inhibit the proliferation of such malignant cells. More recently, new vitamin D3 derivatives have been generated with extraordinarily potent inhibitory effects on leukemic cell growth in vitro. These new data prompted us to (re)investigate the capacity of such new vitamin D3 derivatives to inhibit myeloma cell growth in comparison with that of dexamethasone, a potent antitumoral agent in multiple myeloma. In the current study, we show that EB1089, a new vitamin D3 derivative, (1) induces G1 growth arrest of human myeloma cells, which is only partially reversed by interleukin-6 (IL-6); (2) induces apoptosis in synergy with dexamethasone, IL-6, leukemia-inhibitory factor, and Oncostatin M, with an agonistic anti-gp130 monoclonal antibody being unable to prevent this apoptosis; (3) downregulates both the gp80 (ie, the alpha chain of the IL-6 receptor [IL-6Ralpha]) expression on malignant plasma cells and the production of soluble IL-6Ralpha, and finally (4) inhibits the deleterious upregulation of gp80 expression induced by dexamethasone while limiting the dexamethasone-induced upregulation of gp130 expression. Considering that these in vitro effects of EB1089 have been observed at doses obtainable in vivo (without hypercalcemic effects), our present data strongly suggest that EB1089 could have a true interest in the treatment of multiple myeloma, especially in association with dexamethasone.

Cancer Invest. 1996;14(4):328-34.

Role of vitamin D3 on the activity patterns of hepatic drug metabolizing enzymes in transplantable murine lymphoma.

Sardar S, Chatterjee M, Ghosh S, Roy K.

Vitamin D3 (D3) has been found to exert varied pharmacological actions including restriction of cell growth of a number of malignant cell lines in vitro and inhibition of the promotion of chemical carcinogenesis in mouse skin. In an attempt to confirm the efficacy of D3 as an antineoplastic agent, the present investigation aims at characterizing the importance of D3 in modulating hepatic drug metabolizing enzymes, namely, cytosolic glutathione S-transferase (GSHT), microsomal UDP glucuronyl transferase (UDPGT), and cytochrome P-450, which have been reported by us in recent literature as significant neoplastic markers in mice bearing Dalton's lymphoma (DL). Results show that D3 causes a 150% elevation of GSHT activity and the maintenance of normal, near-control UDPGT activity and cytochrome P-450 content, up to almost 30 days following tumor transplantation, along with bringing about a twofold increase in survival of the host mice. In conclusion, we confirm the definite and significant antitumorigenic role of D3 and its involvement with the discussed hepatic tumor markers in monitoring the processes that lead to cell survival.

Cancer Lett. 2000 Mar 13;150(1):1-13.

Anticlastogenic potential of 1alpha,25-dihydroxyvitamin D3 in murine lymphoma.

Sarkar A, Saha BK, Basak R, Mukhopadhyay I, Karmakar R, Chatterjee M.

Vitamin D3, having gained scientific interest for so long because of its role in mineral homeostasis, has now received great importance as a possible antitumor agent. This study was undertaken in an attempt to visualize the possible anticlastogenic potential of the vitamin in an ascitic mouse lymphoma model namely, Dalton's lymphoma. Frequencies of structural type chromosomal aberrations, sister chromatid exchanges and micronucleus assays have been chosen as the genotoxic endpoints in the proposed investigation. All these cytogenetic markers have been found to be markedly elevated during the progression of lymphoma in bone marrow cells. Vitamin D3 effectively suppressed the frequencies of chromosomal aberrations and sister chromatid exchanges in the lymphoma-bearing mice during the entire phase of tumor growth that significantly coupled with almost two-fold increase in survival time (37 +/- 2 and 68 +/- 2 days in lymphoma controls and vitamin D3-treated lymphoma-bearing mice, respectively), thus substantiating the antineoplastic efficacy of this secosteroid. The outcome of this study also is clearly reflected in the depletion of circulating (serum) vitamin D3 levels in the lymphoma control mice compared with normal (vehicle) controls while a still higher level was maintained in the VD3-treated lymphoma mice. This anticlastogenic property of the vitamin has so far been neglected and this is the first attempt to unravel the vitamin D3's effect in combating tumor development in vivo by limiting the frequencies of chromosomal aberrations, sister chromatid exchanges and micronuclei at least in transplantable murine model studied herein.

Ann Surg Oncol. 1996 Mar;3(2):144-9.

The effect of 1, 25-dihydroxyvitamin D3 on the growth of soft-tissue sarcoma cells as mediated by the vitamin D receptor.

Shabahang M, Buffan AE, Nolla JM, Schumaker LM, Brenner RV, Buras RR, Nauta RJ, Evans SR.

BACKGROUND: Soft-tissue sarcomas, malignant neoplasms originating from mesenchymal tissue, are rare but highly aggressive tumors. Present modes of therapy are associated with high rates of recurrence. 1, 25-Dihydroxyvitamin D3, the active metabolite of vitamin D, serves as a potent antiproliferative agent in human cancer cells. METHODS: In this study, six soft-tissue sarcoma cell lines were analyzed for vitamin D receptor (VDR) expression, which was then correlated with the degree of growth inhibition in response to 1, 25-dihydroxyvitamin D3. These cell lines included rhabdomyosarcoma (HS729, A204), fibrosarcoma (HS913t), synovial sarcoma (SW982), liposarcoma (SW872), and leiomyosarcoma (SKLMS-1). The level of VDR messenger RNA (mRNA) expression was determined using a ribonuclease protection assay, and functional receptor content was determined by using a ligand-binding assay. Growth studies, including [3H]thymidine uptake and growth curves, were performed on two of the six cell lines that expressed the highest and lowest receptor levels. RESULTS: Ribonuclease protection and ligand-binding assays demonstrated variable levels of VDR, with HS729 showing high expression and A204 showing no expression. In HS729, [3H]thymidine uptake was significantly decreased at 10(-7) M (33%) and 10(-6) M (40%) 1, 25-dihydroxyvitamin D3. Growth curve studies showed significant growth inhibition of 55% at 10(-6) M. A204 cells showed no growth inhibition upon treatment with 1, 25-dihydroxyvitamin D3. CONCLUSION: This study demonstrates the existence of VDR in soft-tissue sarcoma cells and suggests a correlation between the level of VDR in cells and the degree of growth inhibition caused by 1, 25-dihydroxyvitamin D3 which may potentially serve as an alternative form of therapy for soft-tissue sarcomas.

Leuk Lymphoma. 1997 Sep;27(1-2):25-33.

Differentiation of myeloid cells and 1,25-dihydroxyvitamin D3.

Takahashi T, Nakamura K, Iho S.

It is well established that 1,25(OH)2D3 induces monocyte/macrophage (Mo/Mphi) colonies when added to culture of granulocyte/macrophage progenitors. Recently, we demonstrated that one of the target cells of 1,25(OH)2D3 in Mo/Mphi differentiation is the neutrophilic promyelocyte that is believed to belong to the neutrophilic lineage. This fact overthrows the established theory that normal hematopoietic precursors are committed to respective cell lineages and do not deviate from their own lineage. The lineage switching from the promyelocyte to Mo/Mphi was suggested to be operating in vivo because 1,25(OH)2D3 is a physiological substance produced by Mphi. More recently, we have shown that transient exposure (24 h) of promyelocytes to 1,25(OH)2D3 causes Mo/Mphi differentiation. This strategy could be useful for examining the effects of 1,25(OH)2D3 on the growth and differentiation of normal myeloblasts and myeloid progenitor cells. Recent advances in molecular biology have enabled investigators to identify a number of genes involved in Mo/Mphi differentiation induced by 1,25(OH)2D3. Some of these may be the determinant genes for Mo/Mphi differentiation; however, further studies are required to determine the underlying mechanisms of Mo/Mphi differentiation.

Br J Nutr. 2003 May;89(5):552-72.

Vitamin D in preventive medicine: are we ignoring the evidence?

Zittermann A.

Vitamin D is metabolised by a hepatic 25-hydroxylase into 25-hydroxyvitamin D (25(OH)D) and by a renal 1alpha-hydroxylase into the vitamin D hormone calcitriol. Calcitriol receptors are present in more than thirty different tissues. Apart from the kidney, several tissues also possess the enzyme 1alpha-hydroxylase, which is able to use circulating 25(OH)D as a substrate. Serum levels of 25(OH)D are the best indicator to assess vitamin D deficiency, insufficiency, hypovitaminosis, adequacy, and toxicity. European children and young adults often have circulating 25(OH)D levels in the insufficiency range during wintertime. Elderly subjects have mean 25(OH)D levels in the insufficiency range throughout the year. In institutionalized subjects 25(OH)D levels are often in the deficiency range. There is now general agreement that a low vitamin D status is involved in the pathogenesis of osteoporosis. Moreover, vitamin D insufficiency can lead to a disturbed muscle function. Epidemiological data also indicate a low vitamin D status in tuberculosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, hypertension, and specific types of cancer. Some intervention trials have demonstrated that supplementation with vitamin D or its metabolites is able: (i) to reduce blood pressure in hypertensive patients; (ii) to improve blood glucose levels in diabetics; (iii) to improve symptoms of rheumatoid arthritis and multiple sclerosis. The oral dose necessary to achieve adequate serum 25(OH)D levels is probably much higher than the current recommendations of 5-15 microg/d.

Br J Cancer. 1996 Jun;73(11):1341-6.

Growth-inhibitory effects of vitamin D analogues and retinoids on human pancreatic cancer cells.

Zugmaier G, Jager R, Grage B, Gottardis MM, Havemann K, Knabbe C.

Retinoids and vitamin D are important factors that regulate cellular growth and differentiation. An additive growth-inhibitory effect of retinoids and vitamin D analogues has been demonstrated for human myeloma, leukaemic and breast cancer cells. We set out to study the effects of the vitamin D analogue EB1089 and the retinoids all-trans- and 9-cis-retinoic acid on the human pancreatic adenocarcinoma cell lines Capan 1 and Capan 2 and the undifferentiated pancreatic carcinoma cell line Hs766T. The cell lines investigated expressed vitamin D receptor, retinoic acid receptor (RAR)-alpha and gamma as determined by polymerase chain reaction after reverse transcription. RAR-beta was expressed only in Hs766T cells. Addition of all-trans-retinoic acid increased the amount of RAR-alpha mRNA in the three cell lines and induced RAR-beta mRNA in Capan 1 and Capan 2 cells. All-trans-retinoic acid at a concentration of 10 nM inhibited the growth of Capan 1 and Capan 2 cells by 40% relative to controls. 9-cis-Retinoic acid was less effective. Neither all-trans-retinoic acid nor 9-cis-retinoic acid affected the growth of Hs766T cells. EB1089, if added alone to the cells, did not significantly inhibit growth. However, the combination of 1 nM EB1089 with 10 nM all-trans-retinoic acid exerted a growth-inhibitory effect of 90% in Capan 1 cells and of 70% in Capan 2 cells. Our data suggest that vitamin D analogues together with retinoids inhibit the growth of human pancreatic cancer cells. However, in vivo studies are necessary to examine the potential use of retinoids and vitamin D analogues on pancreatic cancer.

Cancer Res. 1993 Jun 1;53(11):2534-7.

Antitumor effect of 22-oxa-calcitriol, a noncalcemic analogue of calcitriol, in athymic mice implanted with human breast carcinoma and its synergism with tamoxifen.

Abe-Hashimoto J, Kikuchi T, Matsumoto T, Nishii Y, Ogata E, Ikeda K.

The antitumor effect of 22-oxa-calcitriol (OCT), a newly developed noncalcemic analogue of calcitriol, was examined in vivo in athymic mice implanted with human breast carcinoma with or without estrogen receptor (ER). In ER-positive MCF-7 tumor, the growth of which was dependent on exogenous estrogen, administration p.o. of OCT as well as the antiestrogen tamoxifen five times a week for 4 weeks suppressed tumor growth in a dose-related fashion. The antitumor effect of 1.0 microgram/kg body weight (BW) OCT (mean +/- SEM of tumor weight in 6 mice: 28 +/- 4% of vehicle-treated group) was comparable to that of 2.0 mg/kg BW tamoxifen (25 +/- 6% of control group). In addition, a synergistic antitumor effect of submaximal doses of OCT and tamoxifen was observed in MCF-7 tumor in vivo as well as in ER-positive breast carcinoma cell lines (MCF-7 and ZR-75-1) in vitro. Administration of OCT p.o. three times a week for 4 weeks also suppressed the growth of ER-negative MX-1 tumor in a dose-dependent manner without raising serum calcium concentrations. The antitumor effect of 1.0 microgram/kg BW OCT (mean +/- SEM of tumor weight in 10 mice: 44 +/- 6% of vehicle-treated group) was greater than that of 500 micrograms/kg BW Adriamycin (71 +/- 6% of control group). These results indicate that OCT suppresses the growth of ER-negative as well as ER-positive breast carcinoma in vivo without causing hypercalcemia and that the antitumor effect of OCT can be enhanced by tamoxifen in an ER-positive tumor. It is suggested that OCT may provide a new strategy, either alone or in combination with other anticancer drugs, for systemic adjuvant therapy of breast carcinoma regardless of ER status.

Proc Natl Acad Sci U S A. 1981 Aug;78(8):4990-4.

Differentiation of mouse myeloid leukemia cells induced by 1 alpha,25-dihydroxyvitamin D3.

Abe E, Miyaura C, Sakagami H, Takeda M, Konno K, Yamazaki T, Yoshiki S, Suda T.

Mouse myeloid leukemia cells can be induced to differentiate into macrophages in vitro by 1 alpha,25-dihydroxyvitamin D3, the active form of vitamin D3. The minimal concentration of 1 alpha,25-dihydroxyvitamin D3 to induce the cell differentiation was 0.12 nM. The degree of cell differentiation in various markers induced by 12 nM 1 alpha,25-dihydroxyvitamin D3 was nearly equivalent to that induced by 1 microM dexamethasone, the most potent known stimulator. Among several markers of the differentiation by 1 alpha,25-dihydroxyvitamin D3, phagocytic activity was induced within 24 hr, and this was followed by induction of lysozyme and locomotive activities. Similar changes were also induced by 0.01-1 microM 1 alpha-hydroxyvitamin D3. 25-Hydroxyvitamin D3 and 24R,25-dihydroxyvitamin D3 showed only weak inducing activity. These results suggest the possibility that, in addition to its wellknown biological activities in enhancing intestinal calcium transport and bone mineral mobilization, 1 alpha, 25-dihydroxyvitamin D3 is involved in the differentiation of bone marrow cells.

Mol Cancer Ther. 2004 Mar;3(3):373-81.

Calcitriol in cancer treatment: from the lab to the clinic.

Beer TM, Myrthue A.

1,25-Dihydroxyvitamin D (calcitriol), the most active metabolite of vitamin D, has significant antineoplastic activity in preclinical models. Several mechanisms of activity have been proposed. These include inhibition of proliferation associated with cell cycle arrest and, in some models, differentiation, reduction in invasiveness and angiogenesis, and induction of apoptosis. Proposed mechanisms differ between tumor models and experimental conditions, and no unifying hypothesis about the mechanism of antineoplastic activity has emerged. Synergistic and/or additive effects with cytotoxic chemotherapy, radiation, and other cancer drugs have been reported. Significantly supraphysiological concentrations of calcitriol are required for antineoplastic effects. Such concentrations are not achievable in patients when calcitriol is dosed daily due to predictable hypercalcemia and hypercalcuria; however, phase I trials have demonstrated that intermittent dosing allows substantial dose escalation and has produced potentially therapeutic peak calcitriol concentrations. Recently, a phase II study reported encouraging levels of activity for the combination of high-dose calcitriol and docetaxel administered on a weekly schedule in patients with androgen-independent prostate cancer. This regimen is now under study in a placebo-controlled randomized trial in androgen-independent prostate cancer and in phase II studies in several other tumor types. Further work is needed to elucidate the molecular mechanisms of antineoplastic activity and optimal clinical applications of calcitriol in cancer.

J Biol Chem. 1995 Feb 24;270(8):3642-7.

Protein kinase C and mitogen-activated protein kinase are required for 1,25-dihydroxyvitamin D3-stimulated Egr induction.

Beno DW, Brady LM, Bissonnette M, Davis BH.

Recent studies have demonstrated that 1,25-dihydroxyvitamin D3 (D3) can activate Raf kinase and induce Egr expression in cultured rat hepatic Ito cells (Lissoos, T. W., Beno, D. W. A., and Davis, B. H. (1993) J. Biol. Chem. 268, 25132-25138). Since Raf is an upstream activator of mitogen-activated protein kinase (MAPK), the current study evaluated the ability of D3 to activate MAPK. D3-activated MAPK and induced its cytoplasmic to perinuclear translocation in Ito cells. MAPK activation was found to be protein kinase C-dependent, which was analogous to previous studies of D3 and Raf activation. To further explore the D3 cascade, a series of transient transfections were performed using dominant negative raf and MAPK mutant plasmids which effectively block Ras-induced Raf and MAPK activity, respectively. D3 induced a marked increase in the expression of a chloramphenicol acetyltransferase reporter gene linked to the Egr promoter (egr-CAT). When the dominant negative Raf plasmid was co-transfected, there was no significant reduction in egr-CAT. In contrast, when the dominant negative MAPK plasmid was co-transfected, egr-CAT induction was completely abolished. These results suggest that 1) D3 stimulates MAPK via a protein kinase C-dependent pathway, 2) D3-induced Egr expression can occur via a pathway independent of Ras-induced Raf, and 3) D3 absolutely requires MAPK activity for Egr expression.

J Clin Endocrinol Metab. 1988 Sep;67(3):607-13.

Immunocytochemical detection of 1,25-dihydroxyvitamin D receptors in normal human tissues.

Berger U, Wilson P, McClelland RA, Colston K, Haussler MR, Pike JW, Coombes RC.

We developed an immunocytochemical technique to visualize the receptors for 1,25-dihydroxyvitamin D [1,25-(OH)2D receptor] in cryostat sections of normal human tissues, using a rat monoclonal antibody (9A7 gamma) to the chick intestinal receptor, which has been found to react with mammalian 1,25-(OH)2D receptors. Localization of the antigen was predominantly nuclear, with little cytoplasmic immunoreactivity. Specific staining was seen in the nuclei of many normal epithelial tissues, including liver, kidney, thyroid, adrenal, gastrointestinal tract, breast, and skin. No nuclear staining was seen when tissue sections were incubated with normal rat immunoglobulin G or when the monoclonal antibody was preincubated with a receptor-enriched chick intestinal cytosol preparation. Our results demonstrate that the receptor for 1,25-(OH)2D is localized in the nucleus and widely distributed in normal human tissues.

Endocrinology. 2002 Jul;143(7):2508-14.

Antiproliferative effects of 1alpha,25-dihydroxyvitamin D(3) and vitamin D analogs on tumor-derived endothelial cells.

Bernardi RJ, Johnson CS, Modzelewski RA, Trump DL.

Although there is abundant evidence that 1alpha,25-dihydroxyvitamin D(3) [1,25-(OH)(2)D(3)] inhibits the growth of several cancer cell types, inhibition of angiogenesis may also play a role in mediating the antitumor effects of 1,25-(OH)(2)D(3.) We examined the ability of 1,25-(OH)(2)D(3) to inhibit the growth of tumor-derived endothelial cells (TDECs) and normal endothelial cells and to modulate angiogenic signaling. 1,25-(OH)(2)D(3) inhibited the growth of TDECs from two tumor models at nanomolar concentrations, but was less potent against normal aortic or yolk sac endothelial cells. The vitamin D analogs Ro-25-6760, EB1089, and ILX23-7553 were also potent inhibitors of TDEC proliferation. Furthermore, the combination of 1,25-(OH)(2)D(3) and dexamethasone had greater activity than either agent alone. 1,25-(OH)(2)D(3) increased vitamin D receptor and p27(Kip1) protein levels in TDECs, whereas phospho-ERK1/2 and phospho-Akt levels were reduced. These changes were not observed in normal aortic endothelial cells. In squamous cell carcinoma and radiation-induced fibrosarcoma-1 cells, 1,25-(OH)(2)D(3) treatment caused a reduction in the angiogenic signaling molecule, angiopoietin-2. In conclusion, 1,25-(OH)(2)D(3) and its analogs directly inhibit TDEC proliferation at concentrations comparable to those required to inhibit tumor cells. Further, 1,25-(OH)(2)D(3) modulates cell cycle and survival signaling in TDECs and affects angiogenic signaling in cancer cells. Thus, our work supports the hypothesis that angiogenesis inhibition plays a role in the antitumor effects of 1,25-(OH)(2)D(3).

Clin Cancer Res. 2001 Dec;7(12):4164-73.

Combination of 1alpha,25-dihydroxyvitamin D(3) with dexamethasone enhances cell cycle arrest and apoptosis: role of nuclear receptor cross-talk and Erk/Akt signaling.

Bernardi RJ, Trump DL, Yu WD, McGuire TF, Hershberger PA, Johnson CS.

Previously we have shown that dexamethasone (DEX) enhances the antitumor activity and ligand binding of the active form of vitamin D, 1alpha,25-dihydroxyvitamin D(3) (1,25-D(3)), in the murine squamous cell carcinoma model SCC VII/SF. DEX also reduces the hypercalcemia toxicity of 1,25-D(3) treatment. However, the mechanism of the enhanced antitumor activity has not been defined. Here, we demonstrate that both cell cycle arrest and apoptosis were enhanced by DEX, effects that were inhibited by RU486. We also demonstrate that vitamin D receptor (VDR) protein levels were increased by the combination of 1,25-D(3) and DEX above the level observed with 1,25-D(3) treatment alone, whereas protein levels of the heterodimeric partner of VDR, retinoid X receptor, were lower for the combination than for 1,25-D(3) alone. Glucocorticoid receptor protein levels and ligand binding were increased by 1,25-D(3) but not by the combination. Treatment with the combination of 1,25-D(3) and DEX did not result in greater activation of a vitamin D response element-reporter than 1,25-D(3) alone or of a glucocorticoid response element-reporter than DEX alone. Nevertheless, the levels of phospho-Erk1/2 and phospho-Akt, signaling molecules that are modulated in 1,25-D(3)-treated squamous cell carcinoma cells, were reduced by the combination of 1,25-D(3) and DEX more than by either agent alone. These trends were also observed in vivo. Our results suggest the involvement of the Erk and Akt signaling pathways in the antiproliferative effects of the combination of 1,25-D(3) and DEX and that phospho-Erk1/2 and phospho-Akt may be useful markers of response to this combination.

J Nutr. 2005 Feb;135(2):310-6.

Vitamin D intake: a global perspective of current status.

Calvo MS, Whiting SJ, Barton CN.

Global high prevalence of vitamin D insufficiency and re-emergence of rickets and the growing scientific evidence linking low circulating 25-hydroxyvitamin D to increased risk of osteoporosis, diabetes, cancer, and autoimmune disorders have stimulated recommendations to increase sunlight (UVB) exposure as a source of vitamin D. However, concern over increased risk of melanoma with unprotected UVB exposure has led to the alternative recommendation that sufficient vitamin D should be supplied through dietary sources alone. Here, we examine the adequacy of vitamin D intake worldwide and evaluate the ability of current fortification policies and supplement use practices among various countries to meet this recommendation. It is evident from our review that vitamin D intake is often too low to sustain healthy circulating levels of 25-hydroxyvitamin D in countries without mandatory staple food fortification, such as with milk and margarine. Even in countries that do fortify, vitamin D intakes are low in some groups due to their unique dietary patterns, such as low milk consumption, vegetarian diet, limited use of dietary supplements, or loss of traditional high fish intakes. Our global review indicates that dietary supplement use may contribute 6-47% of the average vitamin D intake in some countries. Recent studies demonstrate safety and efficacy of community-based vitamin D supplementation trials and food staple fortification introduced in countries without fortification policies. Reliance on the world food supply as an alternative to UVB exposure will necessitate greater availability of fortified food staples, dietary supplement use, and/or change in dietary patterns to consume more fish.

Neurochem Int. 1999 Feb;34(2):117-24.

Vitamin D receptor in SH-SY5Y human neuroblastoma cells and effect of 1,25-dihydroxyvitamin D3 on cellular proliferation.

Celli A, Treves C, Stio M.

This study examines the effect of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] on proliferation of SH-SY5Y human neuroblastoma cells and demonstrates, for the first time, the presence of vitamin D receptor (VDR) in this cell line. Cell number showed a significant decrease, when the cells were incubated with 1 or 10 nM 1,25(OH)2D3 for 24, 48, 72, 96 and 144 h, while 100 nM 1,25(OH)2D3 was ineffective after 24 and 96 h incubation. The highest inhibition (about 35%) was observed after 72 h treatment with the hormone at the three concentrations used. Protein content per cell increased, in comparison with controls, after treatment of SH-SY5Y neuroblastoma cells with 1,25(OH)2D3, at the three concentrations, up to 96 h incubation. 1, 10 or 100 nM 1,25(OH)2D3 positively affected [3H]thymidine incorporation after treatment of the cells for 48 and 72 h, while, after 24 h, only 10 nM 1,25(OH)2D3 exerted a stimulatory action. To study the expression of the VDR gene, Northern blot analysis was performed. Subconfluent SH-SY5Y neuroblastoma cells were treated for 24 h with medium containing 10 nM 1,25(OH)2D3 or vehicle alone. A main transcript of an approximate size of 4.5 kb, present either in controls or in cells incubated with the hormone, was revealed. A limited increase in VDR mRNA levels was observed in the cells treated with 1,25(OH)2D3, fetal bovine serum or forskolin. Only slight differences in morphology were perceived between SH-SY5Y cultures maintained with or without 10 nM 1,25(OH)2D3 for 7 days.

Endocrinology. 1981 Mar;108(3):1083-6.

1,25-dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture.

Colston K, Colston MJ, Feldman D.

In this study we demonstrate the presence of specific, high-affinity receptors for 1,25-dihydroxyvitamin D3 in malignant melanoma. Receptors are present both in cultured melanoma cells and in melanoma tumor tissue produced by inoculation of cells into athymic rats. The receptor sediments at 3.25 on sucrose density gradients, possesses a preferential affinity for 1,25-(OH)2D3 and has an apparent Kd of 0.18 nM by Scatchard analysis. We also demonstrate that human melanoma cells are responsive to 1,25-(OH)2D3 in vitro. Inclusion of 1,25-(OH)2D3 in the culture medium produced a marked increase in cell doubling time. This inhibitory effect of the hormone on melanoma cell proliferation was dose-related and represents the first demonstration of a 1,25-(OH)2D3 mediated action on tumor cells.

Biochem Pharmacol. 1992 Aug 18;44(4):693-702.

Effects of synthetic vitamin D analogues on breast cancer cell proliferation in vivo and in vitro.

Colston KW, Chander SK, Mackay AG, Coombes RC.

Calcipotriol (MC903) is a novel vitamin D analogue which effects cellular differentiation and proliferation in vitro and has reduced effects on calcium metabolism in vivo. In the present study its in vitro activity was evaluated using the MCF-7 breast cancer cell line, and its effects on calcium metabolism and mammary tumour growth were measured in vivo in adult female rats. Calcipotriol was compared to the natural metabolite of vitamin D3, 1 alpha,25-dihydroxycholecalciferol [1,25(OH)2D3] and its synthetic analogue 1 alpha hydroxycholecalciferol [1 alpha(OH)D3]. Both calcipotriol and 1,25(OH)2D3 produced significant inhibition of MCF-7 cell proliferation at a concentration of 5 x 10(-11) M. Intraperitoneal administration of calcipotriol to normal female rats showed that the analogue was 100-200 times less active than 1,25(OH)2D3 in raising serum calcium concentration and urinary calcium excretion. Anti-tumour activity of the vitamin D analogues was investigated in vivo using the nitrosomethylurea-induced rat mammary tumor model. Rats, maintained on a low calcium diet, were treated with 1 alpha(OH)D3 (0.25 and 1.25 micrograms/kg). Both doses produced a response rate of 25% but hypercalcaemia developed. Treatment with calcipotriol (50 micrograms/kg) of rats maintained on a normal laboratory diet caused inhibition of tumour progression (response rate 17%) without the development of severe hypercalcaemia. This study supports the concept that vitamin D derivatives may inhibit breast cancer cell proliferation in vivo.

Clin Exp Immunol. 2001 Nov;126(2):214-9.

Effects of vitamin D on the growth of normal and malignant B-cell progenitors.

Consolini R, Pala S, Legitimo A, Crimaldi G, Ferrari S, Ferrari S.

As the effects of vitamin D3, 1,25-dihydroxyvitamin D3 (1,25-(OH)2-D3) (VD, calcitriol) on the proliferation and differentiation potential of normal and leukaemic cells in vitro of myeloid lineage are known, we investigated the response to VD on the growth of both normal and malignant lymphoid progenitors. Effects of vitamin D on normal human lymphoid progenitors and B lineage acute lymphoblastic leukaemia (ALL) progenitors were assessed by using an in vitro cell colony assay specific for either B or T cell lineages. The expression of VDR on B untreated malignant progenitors at diagnosis was investigated by RT-PCR analysis. VD induced a significant inhibition of normal lymphoid cell progenitors growth of both T and B lineage. VD inhibited significantly also the growth of malignant B cell lineage lymphoid progenitors, without inducing cytotoxic effect. As it has been reported that VD effects on activated lymphocytes are mediated by 1,25-(OH)2-D3 nuclear receptor (VDR), we investigated VDR expression on malignant B cell progenitors. We did not detect VDR expression on these cells examined at diagnosis. We demonstrated that VD inhibited in vitro the clonogenic growth of both normal and malignant lymphoid B cell progenitors and that this inhibitory effect on malignant B cell progenitors was not related to VDR. Our work contributes to understanding of the mechanism of action of this hormone in promoting cellular inhibition of clonal growth of malignant lymphoid B cell progenitors, suggesting that the regulation of some critical growth and differentiation factor receptors could be a key physiological role of this hormone.

Br Med J (Clin Res Ed). 1985 Oct 26;291(6503):1153-5.

Alfacalcidol as a modulator of growth of low grade non-Hodgkin's lymphomas.

Cunningham D, Gilchrist NL, Cowan RA, Forrest GJ, McArdle CS, Soukop M.

Ten patients with low grade non-Hodgkin's lymphoma (seven follicular small cleaved and three small lymphocytic) were treated with 1 microgram oral alfacalcidol (1 alpha-hydroxycholecalciferol) daily. Of the seven patients with lymphomas of follicular small cleaved subtype, one achieved complete and three partial remission, whereas none of three patients with small lymphocytic lymphomas responded. In seven of the 10 patients, 1,25(OH)2D3 receptors were measured in tissue from lymph nodes, and a positive correlation between the presence and amount of receptor and response to alfacalcidol was found. These preliminary data suggest that alfacalcidol has appreciable antitumour activity in low grade non-Hodgkin's lymphomas.

J Urol. 1998 Jul;160(1):247-51.

Inhibition of tumor growth and angiogenesis by vitamin D3 agents in murine renal cell carcinoma.

Fujioka T, Hasegawa M, Ishikura K, Matsushita Y, Sato M, Tanji S.

PURPOSE: To investigate the effect of active vitamin D3(VD) agents on tumor growth and metastasis. MATERIALS AND METHODS: BALB/c mice were inoculated with murine renal cancer Renca and graded doses of 1,25-dehydrovitamin D3 or 1- hydrovitamin D3 were given intraperitoneally every other day beginning on day 1, 3, or 7 and ending on day 9, 11, or 15. Direct cytocidal activity and angiogenic activity were evaluated by 48-hour MTT assay and by the colorimetric method, respectively. RESULTS: Both VD agents inhibited tumor growth and prolonged the life span of Renca-bearing mice in a dose-dependent manner and both suppressed tumor growth in athymic mice and euthymic mice with eliminated NK activity. Marginal body-weight loss without appreciable hypercalcemia was observed in mice given VD agents. When treatment was delayed on day 7, the VD agents failed to inhibit tumor growth. The MTT assay showed no direct cytotoxicity of VD agents on Renca. Tumor angiogenesis was inhibited to 46 to 30% of the control level by VD agents. Furthermore, VD agents reduced pulmonary and hepatic foci in the metastatic models. CONCLUSIONS: These results suggest that VD agents may be effective as a treatment for renal cell carcinoma, especially when micrometastases are involved.

Nutr Rev. 2003 Jul;61(7):227-38.

Vitamin D and vitamin D analogs as cancer chemopreventive agents.

Guyton KZ, Kensler TW, Posner GH.

Epidemiologic studies have associated vitamin D, attained through nutrition and sun exposure, with reduced cancer risk. Although dose-limiting hypercalcemia has limited the use of natural vitamin D in cancer prevention, several promising new synthetic vitamin D analogs (deltanoids) are under development. Examples are KH-1060, EB-1089, 1alpha-hydroxyvitamin D5, vitamin D2, and QW-1624F2-2. Clinical targets for deltanoids include colon, prostate, and breast. Studies to elucidate the molecular mechanisms underlying the observed efficacy of deltanoids are ongoing. The vitamin D receptor, a steroid/thyroid receptor superfamily member, appears to control most deltanoid effects on proliferation, apoptosis, differentiation, and angiogenesis.

Biochem Biophys Res Commun. 1998 Aug 28;249(3):735-44.

Combinational effects of vitamin D3 and retinoic acid (all trans and 9 cis) on proliferation, differentiation, and programmed cell death in two small cell lung carcinoma cell lines.

Guzey M, Sattler C, DeLuca HF.

The effects of a combination of vitamin D3 [1,25(OH)2D3] and retinoic acid (RA) on proliferation, differentiation, and apoptosis of the human small cell lung carcinoma (SCLC) cell lines NCI-H82 and NCI-H209 were evaluated. Cell proliferation was inhibited by 1,25(OH)2D3 and RA alone. The combination of 1,25(OH)2D3 and the cis form of retinoic acid resulted in an additive decrease in cell proliferation and the induction of apoptosis in various concentrations. Moreover, 3H-thymidine incorporation was inhibited and the number of viable cells was decreased. The characteristics of the apoptotic cells were examined and confirmed by morphologic analysis, light and electron microscopy, and fluorescence detection. It was concluded that 1,25(OH)2D3 and RA exert additive effects on the inhibition of proliferation and the induction of apoptosis in both the NCI-H82 and the NCI-H209 SCLC cell lines. This finding has important implications for the use of retinoids and 1,25(OH)2D3 in cancer prevention and in the therapy of small cell lung carcinoma.

Anticancer Res. 2001 Jan-Feb;21(1A):321-4.

Oral administration of 1 alpha hydroxyvitamin D3 inhibits tumor growth and metastasis of a murine osteosarcoma model.

Hara K, Kusuzaki K, Takeshita H, Kuzuhara A, Tsuji Y, Ashihara T, Hirasawa Y.

We studied the effect of oral administration of 1 alpha hydroxyvitamin D3 (1-D3) on the growth and metastatic ability of Dunn murine osteosarcoma model. A solution of 1-D3 or vehicle alone was administered daily for 2 weeks to tumor-bearing mice using an esophageal tube and tumor size was serially monitored. In 1-D3-treated mice, the growth of Dunn osteosarcoma was significantly suppressed in a dose-dependent manner. Histologically, tumor cells in the control mice proliferated in marginal regions of the tumor with wide central necrosis, whereas in the 1-D3-treated mice, tumor cells were distributed as scattered islands among extensive necrotic tissue. The mean tumor necrosis area was 55.7% in the control tumors and 94.6% in 1-D3-treated tumors ($p < 0.001$). There were no substantial differences in the cytofluorometric cell cycle distribution or the histological mitotic index between control and 1-D3-treated tumors. When 1-D3 was administered to mice from 2 days before to 2 weeks after transplantation of the tumor, there were significantly fewer metastatic foci in the lungs in 1-D3-treated mice than in control mice. We also tested the effect of coadministration of 1-D3 and doxorubicin on the growth of Dunn osteosarcoma and found that these two drugs act additively to suppress tumor growth. These results indicated that 1-D3 given orally inhibits tumor growth and metastases in a Dunn osteosarcoma model. Although the mechanism remains unknown, oral administration of 1-D3 might be promising as a new method of treating human osteosarcoma.

Rinsho Ketsueki. 1989 Oct;30(10):1876-80.

[1 alpha(OH) D3 (Alfarol) is effective for the treatment of chronic B cell leukemia: a case report]

Hashimoto E, Takeuchi H, Saitou M, Hirashima K.

We reported a case of chronic B-cell leukemia reacted to the administration of 1 alpha (OH)D3 (Alfarol-CHUGAI Pharm. Co.), The patient showed pancytopenia with IgM-kappa type monoclonal protein in the serum. The bone marrow aspiration was failed due to a dry tap, but the biopsied specimen showed a marked infiltration of small sized lymphoid cells with wide cytoplasm. The leukemic cells from peripheral blood showed a morphology of atypical hairy cells, Surface markers of the leukemic cells were IgM, D(kappa)+, CD 19+, CD 20+, CD 21- and HLADR+, The leukemic cells showed no L-tartrate resistant acid phosphatase sensitivity. This case was diagnosed as a chronic B-cell leukemia closely related to a hairy cell leukemia. The treatment with estrogen-chlorambucil compound (Bestrabucil-KUREHA Chem, Co.) or splenic irradiation was not effective. However, after two months' administration of Alfarol the regular blood transfusion was not needed because of increment of the Hb concentration. After eight months of its administration, the bone marrow aspirate showed a marked decrease in the number of the leukemic cells and a restoration of normal hematopoietic cells. This experience suggested that Alfarol in usefull for the treatment of chronic B cell leukemia including hairy cell leukemia and chronic lymphocytic leukemia.