The Role of Vitamin D in Cancer Prevention and Treatment

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KEYWORDS

• Vitamin D • Gene regulation • Antiproliferation
• Antiinflammation • Cancer • Prevention • Treatment

Calcitriol (1,25-dihydroxyvitamin D_3), the biologically most active form of vitamin D, maintains calcium homeostasis through its actions in intestine, bone, kidneys, and the parathyroid glands.[1] The hormone exerts its effects through the vitamin D receptor (VDR), a member of the nuclear receptor superfamily.[1] VDR is present not only in cells and tissues involved in calcium regulation but also a wide variety of other cells including malignant cells. In recent years it has been recognized that calcitriol exerts antiproliferative and prodifferentiating effects in many malignant cells, and retards the development and growth of tumors in animal models raising the possibility of its use as an anticancer agent.[2]

EPIDEMIOLOGY

Epidemiologic studies have noted lower incidence and mortality rates from several cancers in regions with greater solar ultraviolet (UV)-B exposure.[3–5] The potential benefit from sunlight is attributed to vitamin D, because UV light is essential for the cutaneous synthesis of vitamin D.[1] The sunlight hypothesis (assuming that sunlight

This article originally appeared in *Endocrinology and Metabolism Clinics of North America Volume 39, Issue 2, June 2010*.
This work was supported by NCI grant CA130991 and Komen Grant KG080101 (Feldman) and NCI grants CA067267, CA085142, CA095045, and P30 CA016056-32, as well as DOD grant PC040238 (Trump and Johnson).
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Rheum Dis Clin N Am 38 (2012) 161–178
doi:10.1016/j.rdc.2012.03.014 **rheumatic.theclinics.com**
0889-857X/12/$ – see front matter

is a surrogate for vitamin D levels in circulation) has been proposed to determine the risk for several cancers[6,7] including colorectal cancer (CRC)[3] prostate cancer (PCa),[4,5] and breast cancer (BCa).[8] An inverse association between cancer risk and circulating levels of 25-hydroxyvitamin D (25(OH)D, the circulating precursor to calcitriol), which reflect sun exposure and dietary vitamin D intake, has also been reported.[7] The evidence is strongest for CRC; circulating 25(OH)D levels and vitamin D intake are inversely associated with colorectal adenoma incidence and recurrence.[9,10] In addition, higher prediagnosis plasma 25(OH)D levels were associated with a significant improvement in overall survival in CRC patients.[11] A recent reanalysis of data from the Women's Health Initiative (WHI) randomized trial concluded that concurrent estrogen therapy modified the effect of calcium and vitamin D supplementation on CRC risk and in the women assigned to placebo arms of the estrogen trials, the supplementation was beneficial.[12] The evidence is somewhat weaker for PCa, with some studies suggesting an inverse correlation between serum 25(OH)D levels and PCa risk[13,14] although others do not support such a correlation.[15,16] In general, a serum 25(OH)D level exceeding 20 ng/mL was associated with a 30% to 50% reduction in the risk of developing CRC and PCa,[17,18] and a level of approximately 52 ng/mL was associated with a reduction by 50% in the incidence of BCa.[8] Higher dietary intake of vitamin D has been associated with a lower incidence of pancreatic cancer.[19]

MECHANISMS OF THE ANTICANCER EFFECTS OF CALCITRIOL

In addition to the epidemiologic evidence described earlier, data from in vitro studies in cultured malignant cells reveal that calcitriol exerts antiproliferative and prodifferentiating effects; in vivo studies in animal models of cancer demonstrate that calcitriol retards tumor growth.[2,20–31] Several important mechanisms have been implicated in the anticancer effects of calcitriol. The molecular mediators of these calcitriol actions are currently being intensively investigated and characterized.[2]

Growth Arrest and Differentiation

Calcitriol inhibits the proliferation of many malignant cells by inducing cell cycle arrest and the accumulation of cells in the G_0/G_1 phase of the cell cycle.[20,31,32] In PCa cells calcitriol causes G_1/G_0 arrest[26,30,33] in a p53-dependent manner[30] by increasing the expression of the cyclin-dependent kinase inhibitors $p21^{Waf/Cip1}$ and $p27^{Kip1}$,[32–34] decreasing cyclin-dependent kinase 2 (CDK2) activity,[33] and causing the hypophosphorylation of the retinoblastoma protein (pRb).[35] Calcitriol also enhances the expression of p73, a p53 homolog, which has been shown to be associated with apoptosis induction in several human and murine tumor systems. Suppression of p73 abrogates calcitriol-induced apoptosis and reduces the ability of calcitriol to augment the cytotoxic effects of agents such as gemcitabine and cisplatin in a squamous cell carcinoma (SCC) model.[36] Calcitriol also increases the expression of CDK inhibitors in other cancer cells.[2,20,31] It has been shown that calcitriol controls cell growth in part by modulating the expression and activity of key growth factors in cancer cells.[2,20,26,27,30,31] For example, in PCa cells calcitriol up-regulates the expression of insulinlike growth factor binding protein-3 (IGFBP-3),[37,38] which functions to inhibit cell proliferation in part by increasing the expression of $p21^{Waf/Cip1}$.[37]

In many neoplastic cells, calcitriol also induces differentiation resulting in the generation of cells that acquire a more mature and less malignant phenotype. The mechanisms of the prodifferentiation effects of calcitriol in various cancer cells are specific to the cell type and cell context and include, for example, the regulation of signaling pathways involving β-catenin, Jun-N-terminal kinase (JNK), phosphatidyl inositol 3-kinase, nuclear factor κB (NFκB) as well as the regulation of the activity of several transcription