Vitamin D and colon cancer.

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A wealth of scientific evidence supports a role for vitamin D in decreasing colorectal cancer incidence, and possibly mortality. This reduction in risk is related to inhibition of cellular proliferation and stimulation of differentiation. The minimal amount and duration needed to bring about these effects necessitate additional studies. Furthermore, a critical evaluation of physiologically relevant biomarkers of vitamin D status, including 25-hydroxyvitamin D, is needed. Several dietary components and the balance between energy intake and expenditure influence vitamin D metabolism. Scientists need to identify confounders and modifiers of the biological response to vitamin D, including dietary factors, lifestyle factors such as exercise, race or ethnicity, and genetic background.


The effects of 1,25-dihydroxyvitamin D3 on colon cancer cells depend on RhoA-ROCK-p38MAPK-MSK signaling.


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Many studies support a protective action of vitamin D against colon cancer. 1alpha,25-dihydroxyvitamin D3 (1,25(OH)2D3) exerts wide gene regulatory effects in human colon cancer cells. We previously reported that 1,25(OH)2D3 increases cytosolic Ca2+ concentration and transiently activates RhoA and its effector the Rho-associated coiled-kinase (ROCK), and later p38MAPK-MSK. We found that the inhibition of ROCK signaling by Y27632 or that of MSK by Ro318220 prevent the formation of epithelioid islands of SW480-ADH cells by 1,25(OH)2D3 and disrupts the adhesive phenotype of HT29 cells. ROCK and MSK inhibition also abrogates the induction of 1,25(OH)2D3 24-hydroxylase (CYP24), E-cadherin, and vinculin and the repression of cyclin D1 by 1,25(OH)2D3. Moreover, 1,25(OH)2D3 does not promote the localization of the tight junction protein occludin at the plasma membrane in cells expressing a dominant negative RhoA (N19-RhoA). In addition, 1,25(OH)2D3 specifically increases the level of the cysteine protease-inhibitor cystatin D, whereas that of cystatin SN is unaffected. The increase of cystatin D protein caused by 1,25(OH)2D3 is abrogated in N19-RhoA cells. Thus, activation of the RhoA-ROCK-p38MAPK-MSK signaling pathway is essential for the regulation of the phenotype and of the CST5/cystatin D candidate tumor suppressor and other target genes by 1,25(OH)2D3 in colon cancer cells.


Actions of vitamin D are mediated by the TLR4 pathway in inflammation-induced...
colon cancer.

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Many chronic inflammatory diseases are associated with increased risk of developing cancer. In the colon, strong support for a link between chronic inflammation and cancer extends, in part, from population-based studies of persons with inflammatory bowel disease (IBD). Patients with IBD are at increased risk of developing colorectal cancer (CRC). The general consensus is that IBD results from the combined effects of genetics and environment factors known to affect the immune system. Vitamin D, an important regulator of the immune system, has been linked to IBD. Despite the strong potential reported for 1,25-dihydroxyvitamin D (1,25-OH)2D, its effects on calcium metabolism limits its application. Recently, less active vitamin D metabolites, cholecalciferol and 25-hydroxyvitamin D (25(OH)D), have gained considerable attention as promising agents against IBD-related colon cancer. Yet, their anti-proliferative properties and mechanism of action remain to be better defined. We present several signaling pathways commonly regulated by vitamin D compounds and highlight their regulation on TLR4. The efficacy of 25(OH)D and 1alpha-hydroxyvitamin D5 are evaluated using the azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced IBD-related colon carcinogenesis model. In summary, vitamin D supplementation may provide a cost-effective approach to reduce IBD related colon cancer.


Vitamin D receptor ligands, adenomatous polyposis coli, and the vitamin D receptor FokI polymorphism collectively modulate beta-catenin activity in colon cancer cells.

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The activity of beta-catenin, commonly dysregulated in human colon cancers, is inhibited by the vitamin D receptor (VDR), and this mechanism is postulated to explain the putative anti-cancer activity of vitamin D metabolites in the colon. We investigated the effect of a common FokI restriction site polymorphism (F/f) in the human VDR gene as well as the effect of anti-tumorigenic 1,25-dihydroxyvitamin D(3) (1,25D) and pro-tumorigenic lithocholic acid (LCA) VDR ligands on beta-catenin transcriptional activity. Furthermore, the influence of a major regulatory protein of beta-catenin, the APC tumor suppressor gene, on VDR-dependent inhibition of beta-catenin activity was examined. We report herein that beta-catenin-mediated transcription is most effectively suppressed by the VDR FokI variant F/M4 when 1,25D is limiting. Using Caco-2 colorectal cancer (CRC) cells, it was observed that VDR ligands, 1,25D and LCA, both suppress beta-catenin transcriptional activity, though 1,25D exhibited significantly greater inhibition. Moreover, 1,25D, but not LCA, suppressed endogenous expression of the beta-catenin target gene DKK-4 independent of VDR DNA-binding activity. These results support beta-catenin sequestration away from endogenous gene targets by 1,25D-VDR. This activity is most efficiently mediated by the FokI
gene variant F/M4, a VDR allele previously associated with protection against CRC. Interestingly, we found the inhibition of beta-catenin activity by 1,25D-VDR was significantly enhanced by wild-type APC. These results reveal a previously unrecognized role for 1,25D-VDR in APC/beta-catenin cross talk. Collectively, these findings strengthen evidence favoring a direct effect on the Wnt-signaling molecule beta-catenin as one anti-cancer target of 1,25D-VDR action in the colorectum.

Regulation of the colonic vitamin D system for prevention of tumor progression: an update.

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A compromised vitamin D status and nutritional calcium deficit are linked with sporadic colorectal cancer incidence. 25(OH)D(3) serum concentration is a major determinant of 1,25-dihydroxyvitamin D3 (1,25(OH)(2)D(3)) synthesis in colonic mucosa, which expresses the vitamin D receptor and both the synthesizing (CYP27B1) and catabolic (CYP24A1) hydroxylases. Receptor-bound, 1,25(OH)(2)D(3) regulates proliferation, differentiation and apoptosis in an autocrine/paracrine manner. During early malignancy 1,25(OH)(2)D(3) synthesis is often enhanced to counteract hyperproliferation. In many advanced tumors, vitamin D catabolism surpasses synthesis. In vivo, expression and activity of CYP27B1 and vitamin D receptor are stimulated by (phyto)estrogens. Conversely, low nutritional calcium and folate enhance vitamin D catabolism. These insights could explain the lower colorectal cancer incidence in females, the chemopreventive potency of vitamin D and calcium against colorectal cancer, and the benefit of nutritional folate as a methyl donor for epigenetic regulation of the vitamin D system.


Western-style diet-induced colonic tumors and their modulation by calcium and vitamin D in C57Bl/6 mice: a preclinical model for human sporadic colon cancer.

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We reported previously that a new Western-style diet (NWD) for 18 months, consisting of elevated lipids and decreased calcium, vitamin D and methyl-donor nutrients, induced colonic tumors in normal C57Bl/6 mice [Newmark, H.L. et al. (2001) A Western-style diet induces benign and malignant neoplasms in the colon of normal C57Bl/6 mice. Carcinogenesis, 22, 1871-1875], suggesting a new mouse model for human sporadic colon cancer. Here, we have extended this study during a longer feeding period of 2 years wherein tumor formation, tumor inhibition by addition of dietary calcium and vitamin D and their effects on gene expression were determined. We also similarly tested individual supplements of methyl donor (transfer) nutrients (folic acid, choline, methionine and dietary fiber), but these had no significant effect on colonic tumor incidence or multiplicity, whereas supplementation with combined calcium and vitamin D produced significant decrease in both colon tumor incidence and multiplicity, during 2 years of
feeding. No visible colonic tumors were found at 6 months, very few at 12 months, more at 18 months and significantly at 24 months. In a related study of gene changes of the mouse colonic mucosa at 6 months of feeding taken from this study, long before any tumors were visibly detectable, indicated altered profiles of gene expression linked to later risk of dietary initiation of colon tumor formation. This type of early genetic altered profile, an indication of increased risk of later colonic tumor development, may become a useful tool for prediction of colon tumor risk while the colon grossly still appears histologically and physiologically normal.


RhoA-ROCK and p38MAPK-MSK1 mediate vitamin D effects on gene expression, phenotype, and Wnt pathway in colon cancer cells.


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The active vitamin D metabolite 1,25-dihydroxyvitamin D(3) (1,25(OH)(2)D(3)) inhibits proliferation and promotes differentiation of colon cancer cells through the activation of vitamin D receptor (VDR), a transcription factor of the nuclear receptor superfamily. Additionally, 1,25(OH)(2)D(3) has several nongenomic effects of uncertain relevance. We show that 1,25(OH)(2)D(3) induces a transcription-independent Ca(2+) influx and activation of RhoA-Rho-associated coiled kinase (ROCK). This requires VDR and is followed by activation of the p38 mitogen-activated protein kinase (p38MAPK) and mitogen- and stress-activated kinase 1 (MSK1). As shown by the use of chemical inhibitors, dominant-negative mutants and small interfering RNA, RhoA-ROCK, and p38MAPK-MSK1 activation is necessary for the induction of CDH1/E-cadherin, CYP24, and other genes and of an adhesive phenotype by 1,25(OH)(2)D(3). RhoA-ROCK and MSK1 are also required for the inhibition of Wnt-beta-catenin pathway and cell proliferation. Thus, the action of 1,25(OH)(2)D(3) on colon carcinoma cells depends on the dual action of VDR as a transcription factor and a nongenomic activator of RhoA-ROCK and p38MAPK-MSK1.