Epidemiological studies have demonstrated that vitamin D deficiency is associated with various human cancers. Vitamin D receptor (VDR) regulates most of the biological actions of the active vitamin D metabolite, 1α,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃). VDR is highly expressed in small intestine and colon and has critical regulatory actions for proliferation and differentiation, intestinal barrier function, innate immunity, and host defense in the gut. Evidence strongly suggests the protective effects of vitamin D and VDR on colorectal cancer. In this review, we will cover the recent progress of vitamin D/VDR in the genetic regulation, immunity, protein expression, and microbiome, in colon cancer. We will discuss the potential clinical application of vitamin D/VDR in prevention and treatment of colon cancer.

Human vdr Gene Variation and Genetic Regulation in Colon Cancer

The human vdr gene locates on chromosome 12q. It is composed of promoter and regulatory regions (1a–1f) and exons 2–9, which encode 6 domains of the full length VDR protein. When 1,25(OH)₂D₃, also known as calcitriol, binds to VDR protein, VDR is stabilized and translocates to nuclei. VDR associates with the retinoic acid receptor (RXR) through the dimerization domains and plays a role as a transcriptional factor. The 1,25(OH)₂D₃–VDR–RXR complex then binds to the vitamin D response elements through the DNA-binding domain in the promoters of target genes and activates the expression of these target genes.

Using restriction enzymes, polymorphisms of genes are indicated in parentheses. Non-synonymous (FokI) and synonymous (BsmI, Apal, TaqI and Tru9I) single-nucleotide polymorphisms (SNPs) have been identified in vdr gene. These SNPs have been reported to be associated with increased susceptibility to colorectal cancer.¹,² A recent study demonstrated a sex-specific relationship between the vdr polymorphisms and risk for adenomatous polyps (AP), a benign precursor to colon cancer.³ FokI was associated with modified risk for AP in males, whereas the BsmI/Apal/TaqI haplotype was associated with modified risk in females. No interaction was found between vdr gene variants and vitamin D intake.

In a recent study, a genomic workflow integrates the ChIP-Seq data with TCGA expression patterns and patient outcome.⁴ It demonstrated that the commonly reduced expression of the VDR in colon cancer significantly associates with altered expression of vdr target genes. These patterns are associated with significantly worse disease-free survival amongst colon cancer patients.⁴

The Expression Level of VDR Protein in Colon Cancer

There is tissue-type variations in 1,25(OH)₂D₃ signaling. The expression of VDR is an important determinant of the tumor cell response to 1,25(OH)₂D₃. For example, VDR expression increases in hyperplastic polyps and in the early stages of tumorigenesis, but declines in late-stage poorly differentiated tumors and is absent in associated metastases. Tumors of the colon with the highest expression of VDR were most responsive to 1,25(OH)₂D₃ treatment.² However, downregulation of the VDR protein in colon cancer cells reduces the anticancer effect of the vitamin D analog EB1089.² Thus, when we consider the heterogeneity of cancer cells, we need also consider the heterogeneity of VDR and its variability in physiological and pathological conditions in intestine.
**Vitamin D/VDR Regulates Anti-Tumor Immunity in Colorectal Cancer**

1,25(OH)₂D₃ influences neoplastic and immune cells. Immune cells in tumor microenvironment can convert 25-hydroxyvitamin D [25(2)D] to bioactive 1,25(OH)₂D₃. In a nested case–control study (318 rectal and colon carcinoma cases and 624 matched controls) within the Nurses’ Health Study and Health Professionals Follow-up Study using molecular pathological epidemiology database, multivariable conditional logistic regression was used to assess the association of plasma 25(2)D with tumor subtypes according to the degree of lymphocytic reaction, tumor-infiltrating T cells (CD3+, CD8+, CD45RO+ (PTPRC) and FOXP3+ cells), microsatellite instability or CpG island methylator phenotype. This study has demonstrated that high plasma 25(2)D level is associated with lower risk of colorectal cancer with intense immune reaction. It supports the role of vitamin D in cancer immunoprevention.⁵

**Human vdr Gene Variations Shape Microbiome**

The gastrointestinal microbiome is a complex ecosystem with functions in human health and diseases. The vdr gene, as part of the innate immune response, transcribes for antimicrobial peptides and autophagye regulator (for example, ATG16L1),⁶ which are responsible for the deterrence and elimination of infection, and determination of gut microbiome. Further, Wang et al.⁷ reported in *Nature Genetics* that human vdr gene variation is a key host factor influencing the gut microbiome. Intriguingly, our *Gut* paper⁶ also demonstrates that that intestinal epithelial VDR conditional knockout (vdrΔIEC) leads to dysbiosis. We further show that a low intestinal epithelial VDR protein level is associated with impaired autophagy function, accompanied by a reduction in the mRNA and protein levels of ATG16L1, an IBD risk gene and regulator of autophagy and the microbiome. Therefore, the vitamin D/VDR pathway is essential in homeostasis and signaling between the microbiota and host in intestinal inflammation.

**Intestinal Epithelial VDR Regulation of Microbiome in Colon Cancer**

We have shown that absence of intestinal epithelial VDR leads to dysbiosis and susceptibility to colon cancer via reducing JAK/STAT signaling and dampening inflammatory responses.⁸ The JAK/STAT pathway plays a critical role in intestinal and microbial homeostasis. We found that vdrΔIEC mice have higher tumor numbers with tumor location shifted from distal to proximal colon. Fecal microbiota analysis showed that lacking VDR leads to bacterial profile shift from normal to susceptible carcinogenesis. There was enhanced bacterial staining in mouse tumors. These data are consistent with our findings in human tumor sample. VDR deletion decreased JAK2 at protein and mRNA levels. By CHIP assay, we identified that VDR protein bound to the JAK2 promoter, suggesting that VDR transcriptionally regulated JAK2. This study provides new insights into the molecular mechanism of VDR, regulating the JAK/STAT pathway in bacterial-host interactions and tumorigenesis.

**Future Clinical Applications**

Although the vitamin D/VDR in colon cancer is an old topic, the recent research progress in microbiome and genetics brings new insights into the filed. The following areas should be considered for the future clinical application of vitamin D/VDR in prevention and treatment of colon cancer.

- Consider intestinal VDR as a clinical biomarker for identifying patients who might benefit from currently available interventions.
- Develop novel strategies for the prevention and treatment of human colon cancer by restoring the healthy host-microbiome interactions through vitamin D/VDR actions.
- Monitor microbiota and Vitamin D/VDR that may affect the response to colon cancer therapies.
- Explore the novel roles of vitamin D/VDR in other GI cancers?

Vitamin D/VDR will be proved to be a therapeutic target for colon cancer. Understanding the tissue-specific roles of vitamin D/VDR in intestine may offer a diagnostic/prognostic indicator in colon cancer.
CONFLICT OF INTEREST

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