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The Vitamin D Receptor, Inflammatory Bowel Diseases, and Colon Cancer

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Abstract

The nuclear receptor is an emerging therapeutic target in various human diseases. Vitamin D receptor (VDR), a nuclear receptor, mediates the biological functions of vitamin D. Classically, vitamin D is recognized as an essential contributor to mineral and bone homeostasis. Increasing evidence demonstrates that vitamin D is involved in inflammatory responses. Persistent intestinal inflammation is associated with colon cancer. This review focuses on vitamin D and VDR in inflammatory bowel diseases and colon cancer. We place emphasis on the regulatory roles of vitamin D/VDR on in inflammation, enteric bacteria, and tumorigenesis. We summarize the signaling pathways regulated by VDR in intestinal homeostasis. Finally, we discuss the potential application of the insights gleaned from these findings to personalized therapies in chronic inflammation and colon cancer.

Keywords

Colon cancer; inflammation; IBD; nuclear receptor; vitamin D; Vitamin D receptor; gut flora; microbiome; enteric bacteria

Introduction

Vitamin D is known to be involved in calcium and bone development. Since 2000, the public has heard conflicting messages about vitamin D's other benefits in chronic diseases. In 2010, the Food and Nutrition Board of the Institute of Medicine (IOM) released their *Vitamin D Report* [1], increasing the daily recommended intake for vitamin D to 600 IU. The IOM concluded that the evidence supports a role for vitamin D and calcium in bone health but not in other health conditions. Despite the IOM's conclusion, there is widespread enthusiasm regarding the use of vitamin D as an inexpensive and easy supplement for disease prevention and other benefits above and beyond skeletal health.

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In this current review, we will focus on recent progress on the role of vitamin D and its vitamin D receptor (VDR) in anti-inflammatory and anti-proliferative actions, especially in inflammatory bowel diseases (IBD) and colon cancer. Emerging evidence supports the critical roles of vitamin D in controlling inflammation and preventing risks for cancer. We will discuss the potential application of the insights gleaned from these research findings to anti-inflammation, anticancer, and personalized medicine.

Vitamin D and Vitamin D receptor

Vitamin D_3 is synthesized in human skin with sunlight energy. Vitamin D modulates calcium homeostasis and takes part in the regulation of blood pressure, metabolic syndrome, and inflammation [2•,3]. Most of the biological effects of vitamin D are mediated by VDR. Binding of vitamin D_3 to the VDR promotes VDR heterodimerization with the retinoid X receptor and bind cooperatively to vitamin D responsive elements, thus controlling the transcription of target genes. VDR binding sites were significantly enriched near autoimmune and cancer associated genes identified from genome-wide association studies [4••]. Dysfunction of VDR and vitamin D_3 deficiency can cause poor bone development and health, as well as increase the risk of many chronic diseases, such as type 1 diabetes, rheumatoid arthritis, infectious diseases, IBD, and cancer [5–6].

In mammals, VDR is highly expressed in metabolic tissues, such as intestine, kidney, skin, and thyroid gland, and moderately expressed in nearly all tissues. There are differences between human VDR and murine VDR. The antimicrobial peptide cathelicidin is a VDR downstream gene. Only human cathelicidin promoter contains an activating VDRE [7]. The human toll-like receptor (TLR)-induced antimicrobial pathway is distinct from the murine pathway-the human pathway is mediated by the activation of the VDR and Cyp27B1 [8••]. Moreover, there are differences between human and mouse VDR protein. The mouse VDR is five amino acids shorter than human VDR. The homology of the DNA-binding domain (DBD) is 100%, but for the ligand-binding domain (LBD) it is 89%. The homology of the internal region between DBD and LBD, including a portion of LBD, is 55%. These may partly explain the limitations of vitamin D associated murine experimental models.

Vitamin D, VDR, and IBD

IBD comprises ulcerative colitis (UC) and Crohn's disease (CD), which cause chronic inflammation in the digestive tract. The etiology of IBD has been described as interactions among environmental, genetic, and immune factors. The combination of these factors can induce inflammation and subsequent development of mucosal lesions and repair. Interestingly, vitamin D and VDR are involved in these factors in the pathogenesis of IBD.

Environment factors

Vitamin D deficiency may contribute to IBD as an environment factor [2•]. At higher latitudes, cutaneous vitamin D_3 synthesis is insufficient with lower solar ultraviolet B in winter, and without vitamin D rich diets, leads to seasonal variations in circulating vitamin D_3 levels and widespread vitamin D deficiency [9–10]. Prevalence of IBD is higher in the northernmost parts of Europe and America [11]. Patients with IBD have lower serum vitamin D_3 levels than healthy controls [12]. The proportion of vitamin D deficiency in children with IBD was higher than that in healthy controls [13].

VDR gene polymorphisms and expression

The IBD-associated genes are on regions of chromosome 12 and 16. VDR gene locates on the chromosome 12. In human, Fok1, Bsm1, Taq1, Apa1, Cdx2, poly (A), and Bgl1, are associated with risk of IBD [14–15]. VDR expression at mRNA and protein levels is

significantly decreased in IBD patients [16,17•]. In mouse models, VDR expression is required to control inflammation. VDR−/− mice were more susceptible in dextran sodium sulfate-induced colitis [18,19•].

Immune responses

Vitamin D pathway is involved in innate and adaptive immune pathways. Genes encoding cytokines IL-2, IL-10, and IL-12B are primary target genes of vitamin D [20••,21•]. Vitamin D promotes IL-10 production in human B cells. VDR plays a crucial role in innate immune response, which is the body's first line of defense against bacterial pathogens [22]. VDR is required in the development of CD8aa-expressing T Cells [23••]. Th17 and iTreg cells are direct and indirect targets of vitamin D. The increased expression of Th17 cells in the VDR −/− mice was associated with a reduction in tolerogenic CD103(+) dendritic cells. The increased propensity for development of Th17 cells in VDR−/− mice led to more severe IBD in a mouse model [24].

Intestinal Microbiota

Intestinal microbes affect the immune system, supply key nutrients, modulate energy metabolism, stimulate cell growth, repress the growth of harmful microorganisms, and defend against diseases. The target genes of VDR signal include the enzyme Cyp24 and antimicrobial peptides (AMP) [25]. Vitamin D/VDR is responsible for intestinal homeostasis and host protection from bacterial invasion and infection. When the immune system is challenged by pathogens, TGF-beta and IFN-γ are released. Subsequently, VDR is activated to express more cathelicidin and defensin, which are known to regulate the composition of bacterial flora. Additionally, VDR is associated with TLRs, which are expressed to invoke the immune system to recognize bacteria [26•].

VDR−/− mice have increased bacterial loads in the intestine [19•]. Our studies demonstrate that VDR signaling responds to enteric pathogens and commensal bacteria *in vivo* [27]. Reduced vitamin D/VDR levels, an altered number and diversity of gut bacteria, or both will promote inflammation that might disrupt the mucosal barrier and promote food and other allergen sensitization or abnormal tolerization [28]. It is also possible that vitamin D status in intestine determines how gut flora interacts with the immune system [28].

VDR, NOD2, and autophagy are implicated in the pathogenesis of IBD [29, 16, 30]. Vitamin D_3 induces NOD2/CARD15-defensin pathway [31••]. We discussed the link between autophagy and VDR in anti-inflammation in a recent review article [5].

Taken together, synthesis of $1,25(OH)_2D_3$ and VDR status affect the development of colitis. Polymorphisms in the VDR gene and VDR expression are associated with status of IBD. Dysfunction of the vitamin D/VDR signaling is involved in the pathogenesis of IBD. Vitamin D and VDR may affect the composition and functions of gut flora. Hence, restoring vitamin D/VDR signaling may enhance the host’s ability to control inflammation in patients with IBD.

Vitamin D, VDR and colon cancer

Patients with long-term IBD have an increased risk of colorectal carcinoma (CRC)[32–34]. CRC leads to high mortality and accounts for 20% of IBD-related mortality [35]. Epidemiological studies have demonstrated that intensity of local sunlight is inversely correlated with risk of CRC [36]. Adjusted death rates from colon cancer in Caucasian males are nearly three times higher in north eastern states than in sunnier more southerly states in the USA [37]. Inverse associations of CRC risk with dietary vitamin D were found through Meta-analyses. According to a recent review [38], subjects with a serum 25-hydroxyvitamin

D level of 33 ng per milliliter or higher had about half the risk of colorectal cancer than those with levels of 12 ng per milliliter or lower [38].

VDR plays an important role in cellular differentiation and inhibition of proliferation. UC with CRC patients showed lower rate of VDR expression than non-colon cancer patients. Moreover, VDR expression was significantly lower in long-term UC patients (more than ten years), who were at high-risk of developing CRC than short-term patients [17•]. High VDR expression has been reported in early colorectal tumor progression, which is considered as a role for vitamin D inhibiting the paracrine/autocrine growth at the early stage of tumor progression [39]. However, VDR expression is lost during tumor dedifferentiation, which correlates with up-regulation of SNAIL1, a transcriptional repressor of VDR [40•]. In addition, BsmI polymorphism of VDR was associated with a lower CRC risk [41–42].

Tumor cells fail to synthesize the active form of vitamin D and respond to VDR-mediated vitamin D effects. Activation of VDR by vitamin D3 can inhibit tumor cell proliferation by inducing differentiation in various cancer cell lines [43]. VDR knock-out mice showed increased sensitivity to carcinogen challenge [44]. In APCmin/+ mouse mode, VDR may play a suppressive role in intestinal tumor growth via inhibition of β-catenin activity [45].

Some bacteria are considered as pathogens associated with colon carcinoma in many case reports, such as Clostridium septicum, Streptococcus infantarius etc [46]. Patients with UC have lower percentages of potentially protective bacterial species than their healthy twins [47]. A disproportionate increase in some mucolytic bacteria, such as Ruminococcus gnavus and Ruminococcus torques, could be found in normal intestinal epithelium of both CD and UC [48]. Imbalance between different species of enteric bacteria is hypothesized to be one of the risk factors for IBD or CRC.

Interestingly, microorganism infection can disable or hijack the VDR signaling. A number of species have been shown to downregulate the activity of VDR [49]. Borrelia burgdorferi can reduce VDR expression by 50 times in monocytes [49]. The caspases are upregulated by *Shigella* infection that limits the ability of VDR to perform gene transcription [50]. We demonstrated that commensal and pathogenic bacteria directly regulate colonic epithelial VDR expression and location [27]. VDR expression is higher in the proximal colon than in the distal colon, which is correlated with bacterial density and growth [27]. However, the role of vitamin D/VDR in regulating gut flora in tumorigenesis remains unknown.

Vitamin D/VDR regulate response to intestinal immune responses, anti-inflammation, and cancer prevention. VDR dysfunction causes a decline in innate immune function and increases susceptibility to additional infections that contribute to inflammation progression. Hence, it is important to evaluate the associations among VDR, bacterial infection, and colitis-associated colon cancer.

VDR involved signaling pathways in anti-inflammation and anti-proliferation

Inflammatory mediators, such as IL-1, TNF-α, IL-8, nitric oxide, have been shown to be involved in development of inflammation and cancer, especially in the cases of IBD [51••]. Many VDR target genes are involved in dysregulated pathways leading to common human diseases. It is not a surprise that the mechanisms of VDR in IBD and cancer are associated with inflammatory pathways, including NF-kB, JNK, p38, and JAK/STAT (Table 1).

Toll-like receptor

Toll-like receptors (TLRs) are members of the pattern recognition receptor (PRR) family that activates numerous signal-transduction pathways. TLRs provide the host with an immediate and rapid defense against invading microbes in immune response and affects the development of colitis-associated colorectal tumors[52••,53•]. TLRs are considered as regulators in vitamin D/VDR signaling. In human, when a pathogen is detected by TLR, gene expressions of VDR and Cyp27B1 are induced. This leads to 1-α-hydroxylation of 25(OH)D, which is taken up from the blood, and subsequent binding of $1,25(OH)_2D_3$ to VDR [8••]. Inhibition of VDR signaling ablates the TLR-induced antimicrobial activity [8••].

NF-κB

An important TLR downstream effector is the NF-κB transcriptional system that is responsible for the development of colitis and inflammation-linked cancers [54]. Binding of vitamin D/VDR yields a transcription factor that represses NF-κB activation and down-regulates adaptive, but enhances innate immune responses. This product also improves redox balance, thus counterbalancing inflammation on multiple levels. VDR blocks NF-κB by binding to it and preventing it from activating other inflammatory molecules. The interaction of VDR and NF-κB can be modulated by bacteria in the colon [27]. VDR knockout mice exhibited a proinflammatory phenotype-indicated by an increased activity of NF-κB and high serum levels of IL-6 even in the absence of infection [27].

JNK/SAPK and p38 MAP kinases

MAPKs are serine/threonine-specific protein kinases that play a key role in transducing extracellular signals to the nucleus. Four different subgroups have been described including ERKs, JNK/SAPK, BMK1, and p38. Activation of JNK pathway is linked to induction of apoptosis and has been suggested to act as a tumor suppressor. Nevertheless, JNK can also lead to increased proliferation and survival responses of some tumors [55]. The direct binding of VDR to c-Jun is described *in vitro* [56]. Interactions between VDR and JNK/c-Jun pathway contribute to increased VDR activity and subsequent promotion of vitamin D3-induced growth inhibition.

P38 activation induces cell death, which depends on K-ras mutation, in human colon cancer cells. This may occur through AP-1-dependent VDR transsuppression. The sensitivity to p38-induced cell death is determined by the levels of VDR protein concentration in human colon cancer cells [57]. Enhanced VDR expression in K-ras-activated cells inhibits p38 activation-induced cell death [57].

Wnt/β-catenin

Beta-catenin is a key in intestinal proliferation and tumorigenesis. Beta-catenin activity is inhibited by VDR through VDR/β-catenin interaction. Wnt/β-catenin signaling pathway appears to be an important target of the chemopreventive action of vitamin D3 [40•]. Vitamin D3 prevents β-catenin nuclear translocation, leading to inhibition of TCF-4-responsive genes, such as c-myc [58]. Vitamin D3 inhibits β-catenin transcriptional activity by promoting VDR binding to β-catenin and inducing E-cadherin expression. In VDR−/− mice, TCF-4 is decreased. The vitamin D3/VDR-mediated increase in TCF-4 can restrict colorectal cancer cell growth and may have a protective role in colon cancer as well as Crohn's disease [59•].

JAK-STAT

IL-6 signaling via JAK-STAT has been identified as a crucial pathway in colitis-associated neoplasia [60]. Patients with active UC have significantly more IL-6 and pSTAT-3-positive intestinal epithelial cells than patients with inactive UC [61]. IL-23/Th17 pathway plays a critical role in IBD and defenses against different kinds of bacteria. Vitamin D might be beneficial in reducing the development of tumor by inhibiting the action of STAT3 [62]. Mutations in NOD2, which increase risk of colorectal cancer, result in increased production of IL-1β and greater colonic inflammation [63]. However, 1,25D can inhibit STAT signaling to prevent IL-1β production and inhibit the ability of macrophages to induce Wnt signaling in tumor cells in a VDR-dependent manner [64•].

In summary, VDR/vitamin D is involved in multiple pathways that contribute to inflammation and tumorigenesis (Table 1).

Prevention and personalized medicine of vitamin D/VDR in IBD and colon cancer

Genome-wide association studies have uncovered at least 30 genes related to IBD. It will help scientists develop new diagnostic tools and strategies and target-specific therapeutics. However, there is no report on the statuses of vitamin D, the VDR gene, and the efficacy of IBD therapy.

Identifying the K-ras status is the key for an effective therapeutic strategy for colorectal cancer. In colorectal cancer, VDR overexpression is significantly associated with K-ras and PIK3CA mutations. These data support potential interactions between VDR, ras-MAPK, and PI3K-AKT pathways. This indicates possible influence by K-ras or PIK3CA mutation on therapy or chemoprevention targeting [65].

P53 tumor suppressor has been extensively studied in various cancers. Cancer cells often contain abundant mutant p53. Rectal tumors were associated with high levels of calcium overall and p53 tumor mutations. P53 mutations were significantly associated with dietary calcium intake and certain VDR polymorphisms. This indicated an association among calcium, VDR polymorphism, tumors, as well as p53 mutations [66]. Recently, a study on mutated p53 interaction with VDR also indicate that extra caution should be taken in using Vitamin D or its analogs in individualized cancer therapy [67••]

Recent studies demonstrated the efficacy of a potent VDR agonist for the treatment of IBD [68] [69]. The vitamin D analog TX527 directly targets T cells and imprints them with a specific homing signature favoring migration to sites of inflammation [70••]. Serum vitamin D levels and colorectal cancer has an inverse association. New trials assessing moderate-to-high-dose vitamin D supplementation for cancer prevention are in progress [38]. However, the biggest obstacle to clinical use of vitamin D is its potent hypercalcemic effect. Recent papers have also warned against the use of vitamin D in infectious and autoimmune diseases [71;72]. Additional research is required to quantify proper dosage.

Targeting the microenvironment and blocking inflammatory cytokines may represent a promising therapeutic approach for inflammatory diseases. A number of autoimmune diseases can be reversed by gradually restoring VDR function [72]. Preclinical data demonstrate that VDR agonists and BXL-628 (elocalcitol) targeted bladder cells [73]. A recent study provides the proof of concept for the combination of iron chelators and VDR in the treatment of acute myeloid leukemia [74]. There is a long history of using vitamin D to treat mycobacterial infections [75]. Vitamin D_3's antagonism of *M. tuberculosis* involves antimicrobial peptides [8••] and autophagy [76••]. Hence, there is potential to develop a

strategy against chronic inflammatory diseases by combining VDR's synergistic effects with other pathways.

Potential strategies for enhancing the anti-inflammatory ability of vitamin D/VDR can be developed at different levels. These include 1) using vitamin D or its analogs to activate vitamin D/VDR binding; 2) using VDR agonists to enhance VDR signaling; 3) blocking inflammatory cytokines; and 4) targeting the microenvironment and correcting the dysfunction of vitamin D/VDR by using alternative methods, such as probiotics to increase VDR expression in intestine [77].

Overall, experimental models and clinical studies show that vitamin D supplementation or VDR agonists produce therapeutic effects. Moreover, genomics data will identify people at increased risk of diseases and better match patients with effective drugs. Combining with discoveries in genetic and immunological research, we will develop personalized medicine for IBD and cancer therapy. Clinical studies on the effects of calcium and vitamin D3 supplementation, VDR agonists on colitis-associated colon cancer characterized by chronic inflammation are therefore warranted.

Conclusion

VDR has multiple critical functions in regulating response to intestinal homeostasis, immunity, and cell structure [5]. Vitamin D and gut flora may be critical factors that contribute to the pathogenesis of IBD and colon cancer. Dysregulated VDR signaling may explain the mechanism of chronic inflammation (Fig. 1).

Although vitamin D has been extensively studied, many critical questions about the biological functions of VDR, especially intestinal VDR, remain unanswered. For basic research, we need to advance our understanding of 1) the molecular mechanism of vitamin D and VDR in synergistic regulation of inflammatory signaling pathways in experimental models; 2) gut flora and activity of the intestinal VDR; and 3) mechanisms by which intestinal VDR is involved in the pathogenesis of chronic inflammation and colon cancer. For clinical research, new trials assessing moderate- to high-dose vitamin D supplementation for chronic diseases are needed. We need personalized info, such as vitamin D status, VDR expression level, k-ras and p53 status, to optimize clinical outcome. Before we obtain certain and consistent data from clinical studies, it is necessary to make individual treatment decisions [78]. Manipulating the levels of serum and local vitamin D and restoring the function of VDR may represent a new approach to prevention and treatment of chronic diseases.

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Abbreviations

1,25(OH)$_2$D$_3$	Vitamin D$_3$, or cholecalciferol
25(OH)D	25-hydroxyvitamin D, or calcidiol

CD	Crohn's disease
CDAD	*Clostridium difficile*-associated disease
COPD	Chronic obstructive pulmonary disease
EGFR	Epidermal growth factor receptor
HD	Human α defensin
HBD	Human β defensin
HSP	Heat shock proteins
IBD	inflammatory bowel disease
IBS	Irritable bowel syndrome
IκB	Inhibitor of nuclear factor κB
IRAK	interleukin-1 receptor-associated kinase
JAK/STAT	Janus kinase/signal transducers and activators of transcription
MAPK	mitogen-activated protein kinase
(ERK)	extracellular signal-regulated protein kinase
NF	nuclear factor
NOD	Non-obese diabetic mice
RXR	Retinoid X receptor
SAPK/JNK	Stress-activated protein kinase/c-Jun NH2-terminal kinase
TCR	T cell receptor
TID	Type I diabetes
TLR	Toll-like receptor
TNF	tumor necrosis factor
UC	Ulcerative colitis
VDR	Vitamin D receptor, Vitamin D_2 ergocalcifero

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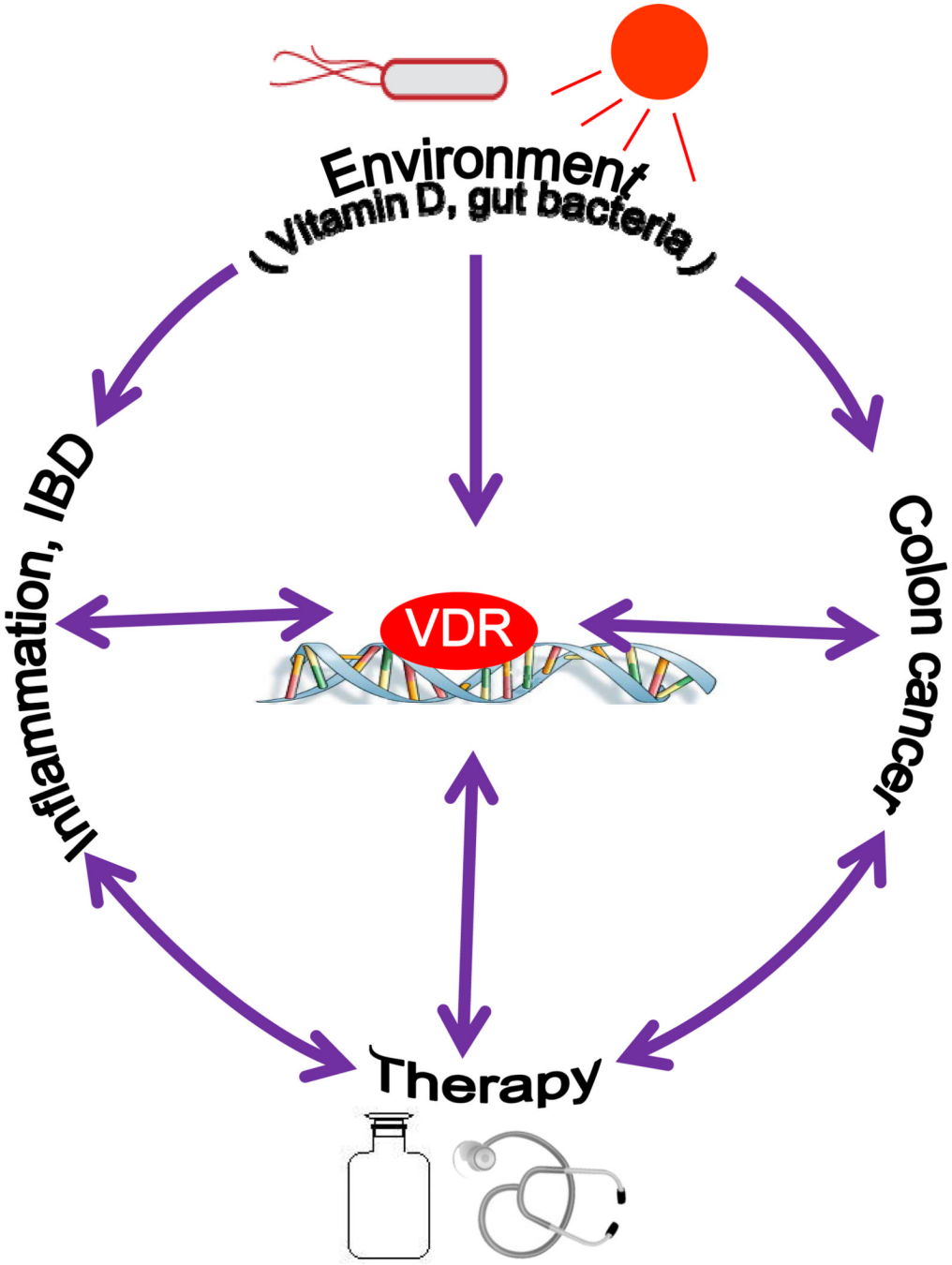

Figure 1.
Vitamin D_3/VDR signaling regulates intestinal homeostasis. Vitamin D and gut flora may be critical factors that contribute to the pathogenesis of IBD and colon cancer. Dysregulated VDR signaling may explain the mechanism of chronic inflammation. Because vitamin D_3/VDR has critical functions in regulating response to intestinal homeostasis, immunity, and cell structure, manipulating the levels of vitamin D and restoring the function of VDR may represent a new approach to prevention and treatment of IBD and colon cancer.

Table 1

Molecular mechanisms of vitamin D/VDR in regulating inflammation and proliferation

Involved pathways	*In vitro* system	*In vivo* system	Summary	Ref.
Toll-like receptors	Human monocytes		Vitamin D_3 down-regulates intracellular TLR-9 expression and TLR-9-induced IL-6 production.	[79]
	MDMs, THP-1		TLR2/1/CD14 stimulation can activate antibacterial autophagy through VDR signaling activation and cathelicidin induction.	[52••]
	Human peripheral monocytes		TLR2/1-induced IL-15 is required for induction of CYP27b1, VDR, and cathelicidin.	[53•]
		C57BL/6 mouse	Influence of vitamin D_3 on TLR-4-L-induced activation of pAPC is dependent on the order of VDR and TLR-4 engagement.	[80]
NF-κB	Caco2, MEF,HT29C19A		LCA down-regulates NF-κB activity through VDR in colonic cancer cells.	[81]
	MEF, Caco2	C57BL/6 VDR(−/−) mouse	VDR negatively regulates bacterial-stimulated intestinal NF-κB activation and attenuates response to infection.	[27]
	HaCaT		Vitamin D_3 decreases NF-κB activity by increasing IκBα levels, and it requires VDR for its action on NF-κB activity	[82]
	HKC,clone-8	mouse	VDR and p65 forms a complex in tubular cells after paricalcitol treatment and paricalcitol inhibits inflammatory infiltration by promoting VDR-mediated sequestration of NF-κB signaling.	[83]
Wnt/β-catenin	HT-29-APC,Caco-2		Vitamin D_3 mediates inhibition of β-catenin transcriptional activity resulting in suppression of β-catenin target genes. Inhibition of β-catenin activity by Vitamin D_3 was enhanced by APC.	[84]
Wnt/β-catenin JAK-STAT	HCT116, Hke-3		Vitamin D_3 blocks the activation of STAT1 and the production of IL-1β in macrophages. Vitamin D_3 inhibits the ability of macrophages to induce Wnt signaling and to promote proliferation of colon cancer cells.	[64]
WNT/β-catenin p38MAPK	SW480, HT29, Caco-2, MCF-7, IMR90,HaCaT, IEC18,,NIH 3T3		Vitamin D_3 activates the p38MAPK and its target MSK1 gene.Activity of these kinases is required for the inhibition of β-catenin–TCF transcriptional activity.	[85•]
JAK-STAT	EOC-20	C57BL/6 and SJL/J	Treatment of activated T cells with vitamin D_3 inhibits the IL-12-induced tyrosine phosphorylation of Stat3.	[86]
JNK p38MAPK	MCF-7, MDA-MB-468		The p38 and JNK pathways cooperate to trans-activate VDR via c-Jun/AP-1 and sensitize cancer cells	[56]

Involved pathways	***In vitro* system**	***In vivo* system**	**Summary**	**Ref.**
			to vitamin D_3-induced growth inhibition.	
p38 MAPK	HCT116		MAPK activation selectively induces cell death in K-ras-mutated human colon cancer cells. Levels of VDR protein concentration affect the sensitivity to p38-induced cell death.	[57]
		rat	Vitamin D_3 activation of p38 MAPK upon aging and abnormal hormone regulation of the c-fos may affect intestinal cell function.	[87]