Vitamin D and Gut Health

9

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Abstract

Vitamin D is a conditionally required nutrient that can either be obtained from skin synthesis following UVB exposure from the diet. Once in the body, it is metabolized to produce the endocrine hormone, 1,25 dihydroxyvitamin D (1,25(OH)2D), that regulates gene expression in target tissues by interacting with a ligand-activated transcription factor, the vitamin D receptor (VDR). The first, and most responsive, vitamin D target tissue is the intestine. The classical intestinal role for vitamin D is the control of calcium metabolism through the regulation of intestinal calcium absorption. However, studies clearly show that other functions of the intestine are regulated by the molecular actions of $1,25(OH)_2$ D that are mediated through the VDR. This includes enhancing gut barrier function, regulation of intestinal stem cells, suppression of colon carcinogenesis, and inhibiting intestinal inflammation. While research demonstrates that there are both classical, calcium-regulating and non-calcium regulating roles for vitamin D in the intestine, the challenge facing biomedical researchers is how to translate these findings in ways that optimize human intestinal health.

Keywords

Vitamin D · Calcium · Absorption · Inflammation · Stem cell · Tight junction · Cancer · VDR

9.1 Introduction

In 1922, E.V. McCollum first coined the term "vitamin D" to describe the fat-soluble vitamin with a critical role in bone health. However, by 1937, work by Nicolaysen made it clear that intestinal calcium absorption is dependent on vitamin D [1] and others showed that intestinal calcium absorption efficiency is reduced by more than 75% during vitamin D deficiency [2, 3]. The molecular era of vitamin D research began when the active metabolite of vitamin D, 1,25 dihydroxyvitamin D ($1,25(OH)_2D_3$) [4, 5], and its nuclear receptor, the vitamin D receptor (VDR) [6], were isolated from the intestinal mucosa. Since then, research on the molecular actions of vitamin D has revealed how $1,25(OH)_2D_3$ acts through the VDR to regulate gene transcription (see [7, 8] for a detailed discussion of this topic). While the highest expression of VDR is seen in the intestinal epithelium [9, 10], VDR protein and VDR-mediated gene expression has been

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identified is many different tissues [11]. In the intestine, VDR gene expression is regulated by glucocorticoids [12] and estrogens [13], increases in the late post-natal period [12, 14], and declines with aging [15, 16]. In this chapter, I will build upon the critical role that vitamin D signaling has on specific intestinal target cells. This information is critical to understand the biological role that vitamin D has on bone health, colon cancer, and inflammatory bowel disease.

9.2 Classical Role of Vitamin D as a Regulator of Intestinal Ca Absorption

A number of studies show that vitamin D-mediated intestinal calcium absorption is the single most important role for vitamin D and VDR during growth. Global VDR gene knockout reduces calcium absorption efficiency by 70% in growing mice [17, 18] and this causes reduced serum calcium, high serum levels of both $1,25(OH)_2D_3$ and PTH, and osteomalacia. Mice with intestine-specific VDR deletion also have the same phenotype as global VDR knockout mice [19], thereby demonstrating the critical importance of intestine for whole body calcium metabolism. As proof of this concept, my research group found that intestine-specific transgenic expression of VDR could normalize calcium absorption efficiency in VDR knockout mice and this was enough to prevent the changes in serum PTH, serum calcium, and bone mineral density that is normally seen in these animals [20].

Careful examination of basal and vitamin D-regulated calcium absorption in rodents and in Caco-2 cells shows that calcium movement across the intestinal barrier occurs through both saturable (transcelluar) and non-saturable (paracelluar) pathways [21–24]. $1,25(OH)_2D_3$ regulates the saturable component of calcium absorption [2, 25–27] and this pathway is energy dependent [28], highest in the proximal small intestine (i.e. the duodenum and proximal jejunum) but also occurs in the large intestine [29–33]. Several groups have shown that VDR expression in the colon is also necessary for normal calcium homeostasis [34, 35] . A comprehensive review of vitamin D mediated Ca absorption is available elsewhere [36].

(a) *Models of vitamin D regulated intestinal Ca absorption:* The best studied model to describe vitamin D-induced Ca absorption is the facilitated diffusion model [37]. In this model, the transient receptor potential cation channel vanilloid family member 6 (TRPV6) mediates basal and vitamin D-induced apical membrane calcium uptake [38–41]. Although $1,25(OH)_2D_3$-induced intestinal calcium absorption was not reduced in TRPV6 knockout mice [42, 43], the increase in calcium absorption induced by a low Ca diet was reduced in mice with a non-functional D541A variant TRPV6 [44]. Also, my group has shown that intestine-specific transgenic expression of TRPV6 increased Ca absorption and recovered the abnormal bone phenotype VDR knockout mice [45], thus proving that TRPV6 is a bona fide mediator of intestinal Ca uptake. The proposed mediator of intracellular diffusion of calcium during absorption is the cytoplasmic calcium binding protein calbindin D_{9k} [37]. However calbindin D_{9k} is not essential for basal or vitamin D regulated Ca absorption [43, 46] and data from a number of studies suggest that calbindins are more likely intracellular calcium buffers than intracellular calcium ferries [47] [41] [45]. The final step in the facilitated diffusion model is the extrusion of calcium from the cell, a process that is mediated by the plasma membrane calcium ATPase 1b (PMCA1b) [28, 48, 49]. Deletion of PMCA1b (Atp2b1) or 4.1R, a protein that stabilizes PMCA1b in the basolateral membrane, reduces both basal and $1,25(OH)_2D_3$-induced intestinal calcium absorption [50, 51].

Several other models for vitamin D regulated intestinal Ca absorption exist and have interesting features, but are less well supported by data than the facilitated diffusions model. In the vesicular transport model, Ca is sequestered into vesi-

cles within the cell as an alternative to the ferry/buffer role proposed for calbindin D. Consistent with a role for vesicles in Ca absorption, $1,25(OH)_2D_3$ treatment increases the number of lysosomes in chick intestine [52], the release of lysosomal enzymes from isolated rat enterocytes [53], the cycling of lysosomes [54], and the level of lysosomal calcium [55]. Although these data support a role for vesicular movement during intestinal Ca absorption, it isn't clear what makes it specific for calcium. Transcaltachia has been described as the rapid absorption of calcium that occurs after exposing chick enterocytes to $1,25(OH)_2D_3$ [56]. Transcaltachia occurs only in response to serosal $1,25(OH)_2D_3$ exposure which suggests either that VDR has a novel membrane signaling role [57] or that transcaltachia is mediated by a multi-functional protein, the membrane associated rapid response steroid binding protein (MARRS) [58]. Intestine-specific deletion of MARRS in mice reduced cellular $1,25(OH)_2D_3$ binding, disrupted $1,25(OH)_2D_3$ regulated calcium and phosphate uptake into isolated enterocytes [59, 60], and reduced basal calcium absorption in by 30% [61]. However, there have been no reported adverse effects of MARRS deletion on bone, despite the critical importance of vitamin D mediated intestinal calcium absorption for normal bone growth [20]. In addition to the transcellular calcium absorption models, some studies show that vitamin D signaling increases paracellular Ca transport in the jejunum and ileum [24, 62, 63] due to $1,25(OH)_2D_3$-mediated induction of two tight junction proteins, claudin 2 and claudin 12 [64]. This may be why non-saturable ileal calcium absorption is reduced in chronic renal disease patients with low serum $1,25(OH)_2D_3$ levels [24].

Finally, we have conducted research that suggests additional mechanisms may control vitamin D-regulated Ca absorption. By using a forward-genetics approach in recombinant inbred lines from a cross of C57BL/6 J and DBA/2 J (BXD) mice, we mapped multiple loci where genetic variation controls intestinal Ca absorption [65]. None of these loci contained genes that encode the proteins that are central to the Ca absorption models described above. As such, our genetic mapping study suggests that novel mechanisms for Ca absorption exist that have not yet been described.

9.3 Gut Absorption and Excretion of Vitamin D

While the intestine is a target organ for $1,25(OH)_2D_3$ action, it is also important for the management of vitamin D status by mediating absorption of dietary/supplemental vitamin D and by mediating the excretion of vitamin D metabolites.

Gastrointestinal and hepatobiliary diseases that cause fat malabsorption also cause vitamin D deficiency in humans [66]. This suggests that vitamin D "follows the fat" during its intestinal absorption, i.e. it is incorporated into micelles, repackaged into chylomicrons, and absorbed into the lymphatic system. Consistent with the "follow the fat" model, when rats were given radiolabeled vitamin D, the label appeared within chylomicrons in the lymph [67–69] and this required the presence of bile acids [70, 71]. In contrast, recent studies show that intestinal absorption of vitamin D may also be an active process that requires the cholesterol transporters SR-BI and NPC1L1 [72]. Regardless of the route of absorption, there doesn't appear to be any regulation of vitamin D absorption. Rats with experimental nephrotic syndrome lose large amounts of vitamin D metabolites in urine and have reduced serum 25OHD levels [73] but even under these conditions, intestinal vitamin D absorption is not elevated. This suggests there is no homeostatic mechanism to upregulate vitamin D absorption in times of need.

There is no evidence to suggest vitamin D_2 and vitamin D_3 are absorbed by different mechanisms. However, 25 hydroxyvitamin D (25OHD) and $1,25(OH)_2D_3$ are absorbed more efficiently than vitamin D [69, 70] and 25OHD is better absorbed than vitamin D in subjects with steatorrhea [74]. This suggests that hydroxylated vitamin D metabolites don't use the fat absorption pathway. Instead, the higher absorption efficiency for 25OHD is due to chylomicro-independent

absorption [70] into the lymph where it is associated with an alpha globulin like the Vitamin D Binding Protein (DBP) [69].

While $1,25(OH)_2$ D can be metabolized to the terminal compound calcitroic acid [75], $1,25(OH)_2$ D can also be sulfonated and glucuronidated in the liver [76, 77]. These metabolites are then excreted through the bile [78], which is the primary route of excretion for vitamin D metabolites. Although the modified $1,25(OH)_2D_3$ forms are not biologically active, the glucuronide residue can be removed by colonic micro-organisms and act locally [79]. This releases the active $1,25(OH)_2D_3$ in the colonic lumen which can then either be reabsorbed (i.e. making an entero-hepatic cycle [80, 81]) or act locally on colonocytes. In fact, while duodenal gene expression is strongly upregulated by increases in circulating $1,25(OH)_2D_3$, colonic gene expression is more strongly upregulated by apical delivery of the hormone [82]. As such, the release of glucuronidated $1,25(OH)_2D_3$ into the bile may be an important mechanism for activating vitamin D mediated gene expression in the colon.

9.4 Cellular Targets of Vitamin D Action in the Intestine

Although the bulk of cells in the intestine are epithelial, it is important to recognize that there is significant diversity in the cell populations that exist within the intestine. At the base of the crypt are multipotent stem cells that give rise to proliferating daughter cells that then receive signals to differentiate into either absorptive epithelial cells or to secretory lineage cells (i.e. goblet cells and enteroendocrine cells) [83]. In addition, underneath the epithelial layer are stromal cells, vascular endothelial cells, and gut associated immune cells. Nonetheless, the bulk of research conducted on vitamin D action in the intestine has focused on the epithelial cells. In this section I will discuss the molecular actions of vitamin D that affect the intestinal epithelium, the stem cells, and, briefly, the gut associated immune cells.

(a) Molecular Targets in Intestinal Epithelial Cells. Before the genomics era, only a few genes involved in intestinal Ca absorption had been examined for transcriptional regulation following $1,25(OH)_2D_3$ -dependent activation of the VDR (e.g. [84, 85]). However, genomic profiling permits a more comprehensive view of vitamin D action on the intestine.

The earliest genomic report was a microarray experiment using $1,25(OH)_2D_3$ -treated (24 h, 100 nM) Caco-2 cells that had been differentiated in culture to resemble the cells of the small intestinal villus [86]. Using an Affymetrix array (12,635 probesets), this report identified 234 probesets that were expressed in all samples, significant at $p < 0.05$, and differentially expressed by vitamin D treatment; only 13 of these probesets (representing 12 distinct genes) changed by more than two-fold. This analysis identified several known vitamin D regulated genes (i.e. CYP24A1) but also potential new vitamin D target genes like amphiregulin, ceruloplasmin, sorcin, and Jun b. As such, this was important "proof of principle" that vitamin D has broader effects on intestinal biology than simply to regulate intestinal Ca absorption.

The largest reported genomic analysis of vitamin D action reported to date is one by Lee et al. [87] who examined the impact of $1,25(OH)_2D_3$ treatment (10 ng/g BW, 6 h) on small intestinal gene expression in CYP27B1 knockout mice using RNA-seq. In mice fed a normal diet, $1,25(OH)_2D_3$ regulated 599 genes while in mice fed a rescue diet to prevent hypocalcemia, it regulated 119 genes. 45 genes were in common across the two diet groups (86% up-regulated), including Cyp24a1, Trpv6, S100G, and Atp2b1. Ion binding was the most enriched GO term for the full vitamin D-regulated gene list, reflecting the large number of mineral transporters that were upregulated. They subsequently looked for enrichment of VDR binding to DNA following $1,25(OH)_2D_3$ treatment (10 ng/g BW, 1 h) of wild-type mice using ChIP-seq. This revealed more than 4000 basal and 17,000 vitamin D-induced VDR binding sites. The genes for the

bulk of the vitamin D regulated transcripts identified in Cyp27b1 KO mice had VDR binding sites associated with them (75% for normal diet, 84% for rescue diet; 87% for the overlapping genes). This included binding sites in all of the traditional intestinal vitamin D target genes (Trpv6, S100g, Apt2b1, Cyp24a1, Cldn2) and for a number of new target genes that includes transporters like Slc30a10 (Mn export), Slc30a1 (the Zn exporter ZnT1), Slc30a5 (the Zn transporter ZnT5) and Slc37a2 (a glucose-6-phosphate transporter), ion channels/sensors like Lrrc26 and Mctp2, and transcription factors like Pdx1, Bach1, and Ppard. The breadth of the functions of these new gene targets suggests vitamin D signaling may control some aspects of lipid metabolism (e.g. Pdx1 and Ppard), mineral toxicity (Slc30a10, Slc30a1, Slc30a5), and the biological response to oxidative stress (Bach1).

Building from the observations of Lee et al. [87], we generated RNA-seq data that reveals vitamin D has distinct gene targets depending upon the state of cell differentiation or the intestinal segment examined. For this, we cultured human duodenal stem cells under conditions that either promote differentiation (to make villus-like enteroids) or to maintain the proliferating stem-cell properties of the culture [88]. When treated with $1,25(OH)_2D_3$ (10 nM, 24 h), the villus-like enteroids had 387 differentially regulated transcripts while the undifferentiated cultures had 130 differentially regulated transcripts; 86 transcripts were in both groups and this overlap group included the classic intestinal vitamin D gene targets. Critically, this experiment demonstrated that intestinal differentiation alters the vitamin D target gene profile and suggests that *in vivo* studies that use mucosal scrapings underestimate the complexity of intestinal vitamin D action. Consistent with this, we have unpublished data that show distinct differences in the vitamin D regulated transcriptome among the small intestine crypts, small intestine villi, and colon epithelium. While this work confirms some of the earlier target genes from Lee et al. [87], it provides more clarity that some gene regulatory events are specific to different functional compartments of the intestine.

(b) Intestinal stem cells

In the base of the crypts of all intestinal segments, 4–8 multipotent Lgr5+ stem cells exist that are the precursor for all of the epithelial cell types in intestine [89]. In the colon, these cells are also where cancer originates [90]. Lgr5+ stem cells express the VDR and are thus vitamin D target cells [91, 92]. Several groups have recently examined how vitamin D signaling impacts the biology of intestinal stem cells. When Peregrina et al. [91] examined the impact of low vitamin D diets (i.e. the New Western Diet 1 or NWD1) or stem cell specific deletion of VDR on Lgr5+ stem cells they found that the these interventions reduced the percentage of Lgr5+ cells (e.g. by 30% after 3 months on the NWD1) and that there were fewer progeny from Lgr5 cells in the villus of these mice. Others have shown that Bmi1+ cells are a reserve stem cell population in the intestine that expands when the Lgr5+ stem cells are damaged (e.g. following radiation) [93]. Consistent with this, Li et al. [94] found that as the NWD1 reduced Lrg5+ cells, it expanded the population of Bmi1+ cells. Feeding the NWD1 also significantly altered the transcript profile of both Lgr5+ and Bmi1+ stem cells. Collectively, these data suggest that vitamin D signaling is required for the maintenance and balance of healthy intestinal stem cell population.

Consistent with a role for vitamin D in the regulation of stem cell biology, Sittipo et al. [95] found that treatment of small intestinal stem cell cultures with $1,25(OH)_2D_3$ for 3 days increased markers of lineage differentiation for goblet cells (Muc2), Paneth cells (Lyz), enteroendocrine cells (Chga), and epithelial cells (Villin). In addition, $1,25(OH)_2D_3$ reduced the number of budding organoids and that this was associated with fewer Ki-67 and Lgr5-labeled cells as well as reduced proliferation and increased apoptosis. Similarly, Fernandez-Barral et al. [92] reported results from an RNA-seq study that shows $1,25(OH)_2D_3$ treatment (10 d, 100 nM) suppressed cell proliferation in human colonic organoids and promoted a differentiated phenotype in colon tumor organoids (3 d, 100 nM). $1,25(OH)_2D_3$-treatment also regulated a wide variety of genes involved in path-

ways that control suppression of proliferation and tumorigenesis, promotion of differentiation, and maintenance of stemness. These data fit the traditional model of $1,25(OH)_2D_3$ as an anti-proliferative, pro-differentiating agent.

(c) Vitamin D regulates tight junctions and barrier function

In addition to its role in regulating nutrient, drug, and fluid movement into and out of the body, the intestine has a primary role in protecting the body by forming tight junctions between cells [96] and acting as a barrier to foreign invaders [97]. A number of studies have clearly shown that vitamin D signaling is crucial to the maintenance of barrier function under normal and inflammatory conditions. The earliest study to make this connection was by Kong et al. [98] who showed that $1,25(OH)_2D_3$ treatment enhanced transepithelial electrical resistance (TEER) in Caco-2 cell monolayers through a VDR-dependent mechanism that induced expression of the tight junction proteins ZO-1 and claudins, 1, 2, and 5. Consistent with a physiological role for this VDR-dependent strengthening of tight junctions, Kong et al. also found that TEER was reduced sooner and more severely in VDR knockout mice following treatment with dextran sulfate sodium (DSS), an agent that damages the epithelium and induces colitis. Several other studies are consistent with a tight junction protective effect of $1,25(OH)_2D$ in intestine. Zhao et al. [99] found that in Caco-2 cells, $1,25(OH)_2D_3$ increased TEER, protein and mRNA levels for tight junction proteins, and decreased monolayer permeability following DSS treatment. Chen et al. [100] later reported that $1,25(OH)_2D_3$ treatment prevented lipopolysaccharide (LPS)-induced Caco-2 cell monolayer damage and prevented LPS-induced redistribution of tight junction proteins.

Several groups have reported that VDR knockout mice are more susceptible to DSS-induced mucosal injury [98, 101, 102]. However, studies in global VDR knockout mice are confounded by the disruption of calcium metabolism and hair loss-related thermoregulation that are central phenotypes to this model. To overcome this problem, we conducted research in two unique mouse models, a mouse with colon-epithelial cell specific deletion of VDR and a VDR knockout mouse with transgenic expression of VDR in the intestinal epithelium [103]. Using these models, we found that intestinal epithelial cell deletion of VDR made the intestinal epithelium more susceptible to DSS induced damage, but that recovery from the damage was normal. In contrast, loss of VDR in the cells outside of the epithelium prevented recovery from DSS-induced barrier damage. Other data from our group [103] and others [101] suggest that intestinal epithelial healing is regulated by innate immune cells like M2 macrophages, and that healing is enhanced by activating $1,25(OH)_2D_3$ signaling in these cells.

(d) Regulation of gut associated immune cells

While the focus of vitamin D action in the intestine has been on its role in modulating epithelial cell function, the intestine also contains a robust mucosal immune system [104]. However, the impact of vitamin D on this system has not been extensively studied. In contrast, there is a body of literature on the role of vitamin D in the regulation of the systemic immune cells (see [105, 106] for overviews) that is driven by the observation that vitamin D deficiency is associated with increased autoimmunity and an increased susceptibility to infection [107].

Although the findings related to the systemic immune system may not apply to the mucosal immune cells, a brief evaluation of vitamin D's impact on systemic immunity is warranted. The vitamin D receptor is expressed in immune cells (e.g. T and B cells, and antigen presenting cells) and when T cells and monocytes/macrophages are activated they can synthesize $1,25(OH)_2D_3$ and use it as an autocrine signal [108–110]. Activation of vitamin D signaling can impact both the innate and adaptive immune responses.

In the innate immune system $1,25(OH)_2D_3$ stimulates differentiation of monocytes to macrophages [111] and regulates genes crucial for autophagy and anti-microbial actions [112–115]. In addition, it reprograms dendritic cells (DC) to become tolerogenic in an inflammatory setting [116] by altering DC differentiation as well as the function of tolerogenic DC [117]. In adaptive immunity, vitamin D may create a more tolerogenic T helper cell profile. However, neither the number nor the type of T cells are grossly abnormal in mice lacking VDR [118]. Similarly, the function of mature T-cells is not strongly influenced by VDR deletion [119, 120]. This suggests that VDR does not have a primary role for normal T-cell development but that $1,25(OH)_2D_3$ may be a modulator of T-cell mediated immune responses. Consistent with this idea, *in vitro* $1,25(OH)_2D$ suppresses NFkB signaling necessary for T_1 helper cell activation [121] and blocks development of Th_{17} and Th_9 cells implicated in the pathogenesis of different types of autoimmunity and inflammatory diseases [122].

The bulk of research on vitamin D and immunity relevant to the intestine has been on vitamin D's role in reducing the severity or duration of colitis and inflammatory bowel disease. This has been reviewed recently elsewhere (see [123]). However, several research groups have examined the role of vitamin D signaling in the biology of type 3 innate lymphoid cells (ILC3), a gut resident immune cell population that participates in innate defense of the intestinal mucosa by producing IL-17 and IL-22 to regulate the production of antimicrobial agents like beta defensin. An early study by Chen et al. [124] showed that global VDR deletion increased ILC3 cell number in small intestine, increased production of antimicrobial peptides, and caused resistance to C. Rodentium infection. However, several later studies have reported opposite findings. Konya et al. [125] found that the pro-inflammatory cytokines IL-23 and IL-6 increased ILC3 VDR expression and that $1,25(OH)_2D$ treatment suppressed IL-22 and IL-17F production by ILC3 cells. He et al. [126] then found that global or ILC3-specific VDR deletion or vitamin D deficiency reduced colonic ILC3 cell number and proliferation while increasing susceptibility to C. Rodentium infection. These findings were confirmed by Lin et al [127] None of these studies characterized the subtype of ILC3. Thus, while it is clear that vitamin D signaling regulates these gut-resident innate immune cells, it is also clear that additional research is necessary to clarify the molecular mechanisms of action in these cells and the physiologic relevance of this regulation.

9.5 Conclusions

In this chapter I reviewed the cellular and molecular actions of vitamin D in the intestine. It has been clear from the beginning of vitamin D research, that the intestine is an important target tissue. The earliest studies on vitamin D and intestine revealed its critical role as a regulator of intestinal calcium absorption, and thus indirectly in the development and maintenance of bone mass. However, genomics studies clearly show that vitamin D has broader intestinal actions that the regulation of calcium absorption. Vitamin D signaling has distinct actions on intestinal stem cells, one undifferentiated crypt cells, on differentiated villus cells, and on gut associated intestinal cells. Thus, in addition to its important role in calcium metabolism, vitamin D also regulates the cell biology of the intestine in ways that protect the stem cell from cancer, limit gut leakiness, and both suppresses epithelial injury, promotes epithelial recovery from injury, and reduces intestinal inflammation (Summarized in Fig. 9.1). Yet while research suggests a variety of important biological roles for vitamin D in the intestine, the challenge facing biomedical researchers is how to translate these findings in ways that optimize human intestinal health.

Conflicts of Interest Dr. Fleet has no conflicts to report.

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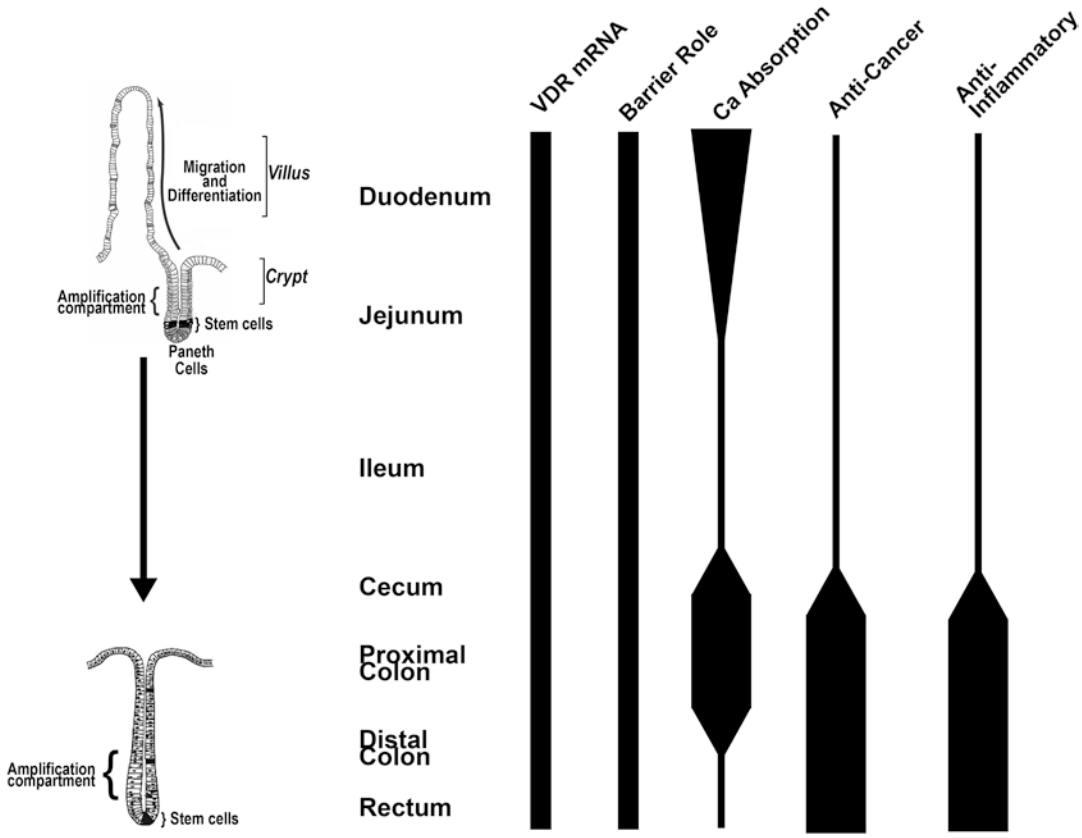

Fig. 9.1 A summary of Vitamin D action across the intestinal tract

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