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Critical Roles of Intestinal Epithelial Vitamin D Receptor Signaling in Controlling Gut Mucosal Inflammation

Yan Chun Li^{1,3}, Yunzi Chen^{1,2}, and Jie Du²

¹Department of Medicine, Division of Biological Sciences, The University of Chicago, Chicago, IL 60637, USA

²Laboratory of Metabolic Disease Research and Drug Development, China Medical University, Shenyang, Liaoning, 110001, China

Abstract

Although vitamin D receptor (VDR) is highly expressed in the intestine, the role of VDR signaling in the gut is not fully understood. Our recent studies unveil a regulatory circuit that centers gut epithelial VDR as a key molecule in the control of mucosal inflammation and colitis development. On the one hand, intestinal epithelial VDR signaling protects the integrity of the mucosal barrier by inhibiting inflammation-induced epithelial cell apoptosis. This barrier-protecting, anti-colitic activity is independent of the non-epithelial immune VDR actions. A healthy and intact mucosal barrier prevents bacterial invasion and thus reduces mucosal inflammation. On the other hand, inflammation in turn down-regulates epithelial VDR expression by inducing VDR-targeting microRNA-346, thus compromising mucosal barrier functions. Consistently, colonic epithelial VDR levels are markedly reduced in patients with inflammatory bowel diseases or in experimental colitis models, whereas vitamin D analog therapy that ameliorates colitis up-regulates epithelial VDR. Thus, gut epithelial VDR signaling appears to play an essential role in controlling mucosal inflammation and thus could be a useful therapeutic target in the management of inflammatory bowel diseases.

Keywords

vitamin D receptor; mucosal barrier; miR-346; TNF-alpha; mucosal inflammation; colitis; intestinal epithelial cells; inflammatory bowel diseases

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³Corresponding author: Yan Chun Li, Ph.D., Department of Medicine, The University of Chicago, 900 E. 57th Street, KCBD 9110, Chicago, IL 60637, USA; Tel: 773-702-2477; Fax: 773-702-2281; cyan@medicine.bsd.uchicago.edu.

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Introduction

The gut, particularly the large intestine, contains an enormous amount of commensal bacteria and other immuno-activating substances in the lumen that can cause mucosal inflammation once invading the lamina propria, where the immuno-activating components of the bacteria activate the immune cells. The gut mucosal epithelial barrier separates the body from the luminal microorganisms and inflammatory and toxic substances. This mucosal barrier consists of a monolayer of epithelial cells with intercellular junctions formed between adjacent cells that seal the paracellular space and regulate permeability of the barrier [1]. Dysfunction of the barrier leads to increased translocation of luminal substances to the lamina propria, triggering inflammatory response [2; 3]. In fact, impaired gut mucosal barrier is a significant pathogenic factor for inflammatory bowel diseases (IBD) [4], the major inflammatory disorders in the gastrointestinal tract in humans that include ulcerative colitis (UC) and Crohn's disease (CD). Mucosal inflammation results in excess production of pro-inflammatory cytokines that can in turn increase mucosal permeability by altering intercellular tight junction structure and induce apoptosis of intestinal epithelial cells (IEC) [4; 5]. Excess IEC apoptosis causes focal disruption of the mucosal barrier independent of the tight junction. Indeed, increased IEC apoptosis has been reported in patients with UC and CD [6; 7; 8] as well as in murine models of colitis [9; 10]. This vicious cycle of mucosal events drives chronic mucosal inflammation and promotes the development of colitis.

Vitamin D hormone is a pleiotropic hormone that has a broad range of biological activities [11]. Vitamin D is converted to the active metabolite 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}_3$) via two steps of hydroxylation in the liver and kidney, and the latter is catalyzed by Cyp27B1, a rate-limiting hydroxylase. Cyp27B1 is also expressed in extra-renal tissues, including the intestine, to drive local production of $1,25(\text{OH})_2\text{D}_3$. Interestingly, colonic Cyp27B1 expression is influenced by Toll-like receptor activation and colonic inflammation [12; 13], but the significance is unclear.

A growing body of epidemiological data has documented an association between vitamin D-deficiency and increased risk of IBD [14; 15; 16], including both CD and UC [17; 18; 19; 20; 21; 22; 23; 24]. A high prevalence of vitamin D deficiency was reported in patients with established as well as newly diagnosed IBD [25; 26; 27]. Vitamin D-deficiency is independently associated with lower quality of life and greater disease activity in IBD [28]. Higher vitamin D status is associated with lowered risk of CD [29]. These observations suggest that vitamin D status might be an environmental determinant for IBD.

The biological activity of $1,25(\text{OH})_2\text{D}_3$ is mediated by the vitamin D receptor (VDR), a member of the nuclear hormone receptor superfamily [30]. VDR is abundantly expressed in the intestine. The classic action of the VDR in the small intestine is to regulate transcellular calcium transport, but its role in the large intestine is less clear. Our recent studies reveal a regulatory circuit that centers gut epithelial VDR as a key molecule in the control of mucosal inflammation and colitis development, suggesting that VDR status might be a key genetic factor influencing IBD development. In this article we summarize these studies.

Potent Anti-colitic Activity of Intestinal Epithelial VDR Signaling

We and other groups have reported that global *VDR* deletion increases mucosal injury that lead to high mortality in dextran sulfate sodium (DSS)-induced experimental colitis model [31; 32; 33]. In this model *VDR*^{-/-} mice showed markedly reduced colonic transepithelial electrical resistance (TER), an indicator of epithelial barrier integrity, before colonic histological abnormalities were seen, suggesting an important role of VDR signaling in maintaining the integrity of the mucosal barrier. Cantorna's group also showed that *VDR*^{-/-}/*IL-10*^{-/-} mice developed more severe colitis and higher mortality than *VDR*^{+/+}/*IL-10*^{-/-} mice [34]. These observations, however, could not distinguish the relative contribution of epithelial versus immune VDR signaling in the regulation of mucosal inflammation. Therefore, recently we used a transgenic (Tg) approach to specifically address the role of gut epithelial VDR in the pathogenesis of colitis [35], and we discuss this study in detail below.

We used the 12.4 kb *villin* promoter [36] to target a FLAG-tagged human (h) VDR transgene [37] to the IECs in a C57BL/6 background. The resultant Tg mice exhibited 2- to 3- fold increase in VDR expression throughout the intestinal epithelia relative to wild-type (WT) control mice, but the hVDR transgene had no obvious effects on the morphology or cellular proliferation of the intestine. One striking phenotype of these Tg mice is that they are extremely resistant to colitis. We examined these mice using a number of colitis models, including DSS-induced colitis model, 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis model, adoptive T cell transfer model of chronic colitis and *IL-10*-deficient spontaneous colitis model, and without exception, in all these models the Tg mice exhibited markedly attenuated mucosal inflammation and reduced mucosal injury at morphological and histological levels compared to WT mice. The disease symptoms of the Tg mice were much less severe than the WT controls [35]. We chose to test the Tg mice in different colitis models because none of the mouse colitis models currently used in the field can completely recapitulate all the features of IBD in humans. Among these models, the DSS model resembles human ulcerative colitis with respect to loss of barrier function [38], and the TNBS model is thought to resemble Crohn's disease because it involves T_H1-mediated mucosal inflammation [39]. The adoptive T cell transfer model, which involves transfer of naïve CD4⁺CD45RB^{high} T cells into a *Rag1*^{-/-} background, is believed to best recapitulate the clinical and histological characteristics of human IBD [40; 41]. This method was also used by Cantorna's group to study colitis development in *VDR*^{-/-} mice [34]. *IL-10*^{-/-} mice develop spontaneous chronic intestinal inflammation due to aberrant immune response [42; 43], a model widely used in colitis research. Based on data from these colitis models, we can conclude with strong confidence that the intestinal epithelial VDR signaling inhibits mucosal inflammation and protects against colitis.

Rescue of Severe Colitis Phenotype of VDR-null Mice with the hVDR Transgene

We previously showed that *VDR*^{-/-} mice developed severe colitis and high mortality in the DSS model [32], but because of the global deletion of the *VDR* gene, the role that the epithelial and non-epithelial VDR plays in colitis development is unknown. We reasoned that, if the anti-colitic activity of the epithelial VDR is a primary and essential protective

mechanism, then reconstitution of the gut epithelial cells in *VDR*^{-/-} mice with the hVDR transgene should be able to prevent or attenuate the severe colitic phenotype seen in *VDR*^{-/-} mice. Indeed, when we introduced the hVDR transgene to the *VDR*^{-/-} gut epithelial cells through breeding of villin-hVDR Tg mice and *VDR*^{-/-} mice, the modified *VDR*^{-/-} mice with hVDR expressed only in the IECs behaved almost like the Tg mice in TNBS and DSS models and were highly resistant to colitis, whereas the parental *VDR*^{-/-} mice developed very severe colitis and most died within a few days into the experiment [35]. Therefore, even though *VDR*^{-/-} mice have a hyper-responsive immune system as we had reported [44], restoring of epithelial VDR signaling is sufficient to inhibit mucosal inflammation and block colitis development. These observations confirm a critical and predominant role of the epithelial VDR signaling in preventing mucosal inflammation that is independent of VDR activities originated from the non-epithelial immune system.

Mucosal Barrier-Protecting Mechanism of Intestinal Epithelial VDR Signaling

In IBD colonic mucosal permeability is usually increased before clinical symptoms or histological damage are developed. We observed that, in contrast to WT controls, the colonic mucosal transepithelial electrical resistance (TER), an indicator of mucosal permeability, was well preserved in the villin-hVDR Tg mice in the early stage of colitis [35], indicating that epithelial hVDR signaling protects the integrity of the mucosal epithelial barrier. Increased apoptosis in gut epithelial cells is a leading cause of elevated mucosal permeability. In fact, TNF- α and IFN- γ , two cytokines critical to IBD pathogenesis, induce IEC apoptosis [5]. We observed that, whereas *VDR*^{+/+} and *VDR*^{-/-} mice exhibited abundant apoptotic epithelial cells in colitis models, the hVDR transgene markedly reduced IEC apoptosis in either *VDR*^{+/+} or *VDR*^{-/-} background. Consistently, the hVDR transgene also suppressed caspase 3 activation and down-regulated the expression of p53-upregulated modulator of apoptosis (PUMA), a key mediator of IEC apoptosis in IBD [45]. PUMA is a BH-3 domain pro-apoptotic Bcl-2 family member that interacts with anti-apoptotic Bcl-2 family members to activate pro-apoptotic Bax and Bak and trigger mitochondrial dysfunction. This results in the release of several apoptogenic mitochondrial proteins such as cytochrome c, leading to caspase activation and cell death [46].

In the colon PUMA is transcriptionally induced by NF- κ B in a p53-independent manner to mediate TNF α -induced apoptosis [47; 45]. We have shown that 1,25(OH)₂D₃ suppresses TNF α -induced NF- κ B activity [48], and ligand-activated VDR blocks NF- κ B activation by directly interacting with IKK β [44]. We confirmed that in human colonic cancer cells 1,25(OH)₂D₃ attenuated TNF α -induced PUMA expression by blocking NF- κ B binding to the *PUMA* gene promoter. Furthermore, we observed that intestinal epithelial hVDR overexpression in the transgenic mice markedly suppressed colonic mucosal IKK kinase activity induced during colitis development, concomitant with the blockade of mucosal caspase 3 activation and PUMA induction [35]. These data demonstrate that intestinal epithelial VDR signaling plays a key role in maintaining mucosal barrier integrity by suppressing IEC apoptosis, thus suppressing mucosal inflammation.

Reduced Colonic Epithelial VDR in IBD Patients

Given the mucosal barrier-protecting role for VDR, it is conceivable that epithelial VDR reduction increases the risk of mucosal barrier dysfunction and promotes mucosal inflammation. Indeed, we found that epithelial VDR levels are substantially reduced in patients with IBD [35; 49]. We examined the VDR status in colonic biopsies from both CD and UC patients in comparison with normal colon samples in two cohorts, one from Chicago, USA and the other from Shenyang, China. In the Chinese cohorts we were able to compare biopsies from lesions and adjacent normal tissues within the same patients. Immunostaining, Western blotting and cDNA microarray data all showed that VDR levels were reduced by >50% in the lesion, whereas pro-inflammatory cytokines (such as TNF α and IL-1 β) were elevated. This observation suggests that local inflammation might have a repressive effect on epithelial VDR expression.

MicroRNA-mediated Mechanism for Inflammation-induced VDR Down-regulation

Based on the animal and human data we reasoned that epithelial VDR reduction likely compromises the gut mucosal barrier and contributes to the development of IBD. Therefore, it is important to understand the molecular mechanism underlying the down-regulation of epithelial VDR in colitis. To test the hypothesis that inflammation down-regulates VDR expression, we examined the effect of several pro-inflammatory cytokines (TNF- α , IL-1 β and IL-6) on VDR expression in colon cancer cells, and found that TNF- α can suppress VDR by about 50-60% [49], a decrease similar to what is seen in IBD patients [35]. This result is very relevant because TNF- α is a major inflammatory cytokine involved in the pathogenesis of IBD, and anti-TNF therapy is widely used in IBD management [50; 51].

Interestingly, we found that, while down-regulating VDR, TNF- α concomitantly induced miR-346 and miR-125b. MicroRNAs (miRNAs) are naturally occurring small non-coding RNAs that control target genes by translational repression or mRNA degradation [52; 53]. Previous studies showed that miR-125b targets VDR [54]. By *in silico* analysis we identified a putative binding site for miR-346 within the 3' untranslated region (UTR) of hVDR transcript. Therefore, TNF- α might suppress VDR via inducing miR-346 and/or miR-125b. However, using miRNA hairpin inhibitors to inhibit miR-125b or miR-346, we concluded that miR-346, not miR-125b, likely mediates the repressive effect of TNF- α on VDR expression.

We went on to confirm that miR-346 indeed directly targets VDR via the target site within its 3'UTR [49]. In fact, the target sequence for human and mouse miR-346s are highly conserved within mouse and human VDR 3'UTR, respectively. In cell culture, miR-346 oligo mimic could substantially reduce hVDR expression (by >50%) as well as VDR transactivating activity. The specific target site in the 3'UTR was required to mediate the suppression of VDR by miR-346, and the activity was disrupted when the 3'UTR target site was mutated. These data demonstrate that VDR is a direct target of miR-346.

We also assessed the relevance of the regulatory relationship among colonic inflammation, miR-346 and epithelial VDR in IBD patients as well as in experimental colitis models. Human UC lesion biopsies contained massive infiltration of CD4⁺ and CD11b⁺ cells as well as TNF- α -producing cells in the lamina propria. TNF- α and miR-346 expression was dramatically induced, whereas VDR expression decreased by >50%, relative to adjacent normal tissues. In IL-10^{-/-} mice with spontaneous colitis, colonic mucosal VDR levels were dramatically reduced. In TNBS-induced colitis model, colonic mucosal VDR levels gradually decreased with the progression of mucosal inflammation, which was accompanied by a dramatic induction of TNF- α and miR-346 in the mucosa during this period [49]. These observations are consistent with the conclusion that TNF- α down-regulates VDR via inducing miR-346.

Discussion and Conclusion

Taken together, our recent studies unveil a critical role of intestinal epithelial VDR in the regulation of mucosal inflammation. Whereas the VDR signalling maintains the integrity of the mucosal barrier by inhibiting inflammation-induced apoptosis of intestinal epithelial cells, VDR abundance is influenced by mucosal inflammation in turn, as its expression is down-regulated by mucosal pro-inflammatory cytokines. Thus, epithelial VDR appears to be a central molecule in a regulatory circuit controlling mucosal inflammation (Figure 1). Reduction in intestinal epithelial VDR levels promotes mucosal inflammation and likely increases the risk of colitis, whereas raising epithelial VDR levels by vitamin D analogue therapy or by anti-TNF therapy might have important therapeutic value in the management of IBD. In fact, vitamin D hormone not only can induce VDR expression [55], but also suppresses TNF- α production [44]. Thus in theory vitamin D therapy can shift the balance to favor inhibition of inflammation and blockade of IEC apoptosis. This could be a mechanism by which vitamin D therapy ameliorates IBD.

Our studies suggest that the epithelial VDR signaling may function as a primary defense mechanism to suppress colonic inflammation by protecting the mucosal barrier. However, as a pleotropic hormone vitamin D-VDR signaling may regulate mucosal inflammation in multiple ways. For example, vitamin D could influence colonic commensal bacterial profiles through regulation of anti-microbial peptides [56; 57; 58]. Epithelial VDR signaling may also regulate autophagy, another molecular event that has been implicated in IBD [59; 60; 61]. Finally, as a well-known immune regulatory factor, vitamin D-VDR signaling can certainly control mucosal inflammation by regulating the immune system [62; 63]. Therefore, it is conceivable that the anti-colitic mechanism of epithelial VDR signaling could be multifactorial and not limited to the regulation of barrier function.

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References

1. Laukoetter MG, Bruewer M, Nusrat A. Regulation of the intestinal epithelial barrier by the apical junctional complex. *Curr Opin Gastroenterol.* 2006; 22:85–89. [PubMed: 16462161]

2. Fasano A, Shea-Donohue T. Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. *Nat Clin Pract Gastroenterol Hepatol*. 2005; 2:416–422. [PubMed: 16265432]
3. Watson AJ, Chu S, Sieck L, Gerasimenko O, Bullen T, Campbell F, McKenna M, Rose T, Montrose MH. Epithelial barrier function in vivo is sustained despite gaps in epithelial layers. *Gastroenterology*. 2005; 129:902–912. [PubMed: 16143130]
4. Gibson PR. Increased gut permeability in Crohn's disease: is TNF the link? *Gut*. 2004; 53:1724–1725. [PubMed: 15542502]
5. Edelblum KL, Yan F, Yamaoka T, Polk DB. Regulation of apoptosis during homeostasis and disease in the intestinal epithelium. *Inflamm Bowel Dis*. 2006; 12:413–424. [PubMed: 16670531]
6. Iwamoto M, Koji T, Makiyama K, Kobayashi N, Nakane PK. Apoptosis of crypt epithelial cells in ulcerative colitis. *J Pathol*. 1996; 180:152–159. [PubMed: 8976873]
7. Hagiwara C, Tanaka M, Kudo H. Increase in colorectal epithelial apoptotic cells in patients with ulcerative colitis ultimately requiring surgery. *J Gastroenterol Hepatol*. 2002; 17:758–764. [PubMed: 12121505]
8. Di Sabatino A, Ciccocioppo R, Luinetti O, Ricevuti L, Morera R, Cifone MG, Solcia E, Corazza GR. Increased enterocyte apoptosis in inflamed areas of Crohn's disease. *Dis Colon Rectum*. 2003; 46:1498–1507. [PubMed: 14605569]
9. Nenci A, Becker C, Wullaert A, Gareus R, van Loo G, Danese S, Huth M, Nikolaev A, Neufert C, Madison B, Gumucio D, Neurath MF, Pasparakis M. Epithelial NEMO links innate immunity to chronic intestinal inflammation. *Nature*. 2007; 446:557–561. [PubMed: 17361131]
10. Frey MR, Edelblum KL, Mullane MT, Liang D, Polk DB. The ErbB4 growth factor receptor is required for colon epithelial cell survival in the presence of TNF. *Gastroenterology*. 2009; 136:217–226. [PubMed: 18973758]
11. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, Lieben L, Mathieu C, Demay M. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev*. 2008; 29:726–776. [PubMed: 18694980]
12. Liu N, Nguyen L, Chun RF, Lagishetty V, Ren S, Wu S, Hollis B, DeLuca HF, Adams JS, Hewison M. Altered endocrine and autocrine metabolism of vitamin D in a mouse model of gastrointestinal inflammation. *Endocrinology*. 2008; 149:4799–4808. [PubMed: 18535110]
13. Mukherji A, Kobiita A, Ye T, Chambon P. Homeostasis in Intestinal Epithelium Is Orchestrated by the Circadian Clock and Microbiota Cues Transduced by TLRs. *Cell*. 2013; 153:812–827. [PubMed: 23663780]
14. Loftus EV Jr, Sandborn WJ. Epidemiology of inflammatory bowel disease. *Gastroenterol Clin North Am*. 2002; 31:1–20. [PubMed: 12122726]
15. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology*. 2004; 126:1504–1517. [PubMed: 15168363]
16. Lim WC, Hanauer SB, Li YC. Mechanisms of Disease: vitamin D and inflammatory bowel disease. *Nature Clinical Practice Gastroenterology & Hepatology*. 2005; 2:308–315.
17. Scharla SH, Minne HW, Lempert UG, Leidig G, Hauber M, Raedsch R, Ziegler R. Bone mineral density and calcium regulating hormones in patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis). *Exp Clin Endocrinol*. 1994; 102:44–49. [PubMed: 8005208]
18. Bischoff SC, Herrmann A, Goke M, Manns MP, von zur Muhlen A, Brabant G. Altered bone metabolism in inflammatory bowel disease. *Am J Gastroenterol*. 1997; 92:1157–1163. [PubMed: 9219790]
19. Marx G, Seidman EG. Inflammatory bowel disease in pediatric patients. *Curr Opin Gastroenterol*. 1999; 15:322–325. [PubMed: 17023965]
20. Jahnsen J, Falch JA, Mowinckel P, Aadland E. Vitamin D status, parathyroid hormone and bone mineral density in patients with inflammatory bowel disease. *Scand J Gastroenterol*. 2002; 37:192–199. [PubMed: 11843057]
21. Schulte CM. Review article: bone disease in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2004; 20(Suppl 4):43–49. [PubMed: 15352893]

22. Pappa HM, Gordon CM, Saslowsky TM, Zholudev A, Horr B, Shih MC, Grand RJ. Vitamin D status in children and young adults with inflammatory bowel disease. *Pediatrics*. 2006; 118:1950–1961. [PubMed: 17079566]
23. Sinnott BP, Licata AA. Assessment of bone and mineral metabolism in inflammatory bowel disease: case series and review. *Endocr Pract*. 2006; 12:622–629. [PubMed: 17229657]
24. Souza HN, Lora FL, Kulak CA, Manas NC, Amarante HM, Borba VZ. Low levels of 25-hydroxyvitamin D (25OHD) in patients with inflammatory bowel disease and its correlation with bone mineral density. *Arq Bras Endocrinol Metabol*. 2008; 52:684–691. [PubMed: 18604382]
25. Driscoll RH Jr, Meredith SC, Sitrin M, Rosenberg IH. Vitamin D deficiency and bone disease in patients with Crohn's disease. *Gastroenterology*. 1982; 83:1252–1258. [PubMed: 6982188]
26. Harries AD, Brown R, Heatley RV, Williams LA, Woodhead S, Rhodes J. Vitamin D status in Crohn's disease: association with nutrition and disease activity. *Gut*. 1985; 26:1197–1203. [PubMed: 3877663]
27. Vogelsang H, Ferenci P, Woloszczuk W, Resch H, Herold C, Frotz S, Gangl A. Bone disease in vitamin D-deficient patients with Crohn's disease. *Dig Dis Sci*. 1989; 34:1094–1099. [PubMed: 2743850]
28. Ulitsky A, Ananthakrishnan AN, Naik A, Skaros S, Zadvornova Y, Binion DG, Issa M. Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life. *JPEN J Parenter Enteral Nutr*. 2011; 35:308–316. [PubMed: 21527593]
29. Ananthakrishnan AN, Khalili H, Higuchi LM, Bao Y, Korzenik JR, Giovannucci EL, Richter JM, Fuchs CS, Chan AT. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. *Gastroenterology*. 2012; 142:482–489. [PubMed: 22155183]
30. Haussler MR, Whitfield GK, Kaneko I, Haussler CA, Hsieh D, Hsieh JC, Jurutka PW. Molecular mechanisms of vitamin D action. *Calcif Tissue Int*. 2013; 92:77–98. [PubMed: 22782502]
31. Froicu M, Cantorna MT. Vitamin D and the vitamin D receptor are critical for control of the innate immune response to colonic injury. *BMC Immunol*. 2007; 8:5. [PubMed: 17397543]
32. Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, Bissonnette M, Li YC. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. *Am J Physiol Gastrointest Liver Physiol*. 2008; 294:G208–216. [PubMed: 17962355]
33. Kim JH, Yamaori S, Tanabe T, Johnson CH, Krausz KW, Kato S, Gonzalez FJ. Implication of intestinal VDR deficiency in inflammatory bowel disease. *Biochim Biophys Acta*. 2013; 1830:2118–2128. [PubMed: 23041070]
34. Froicu M, Weaver V, Wynn TA, McDowell MA, Welsh JE, Cantorna MT. A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. *Mol Endocrinol*. 2003; 17:2386–2392. [PubMed: 14500760]
35. Liu W, Chen Y, Golan MA, Annunziata ML, Du J, Dougherty U, Kong J, Musch M, Huang Y, Pekow J, Zheng C, Bissonnette M, Hanauer SB, Li YC. Intestinal epithelial vitamin D receptor signaling inhibits experimental colitis. *J Clin Invest*. 2013; 123:3983–3996. [PubMed: 23945234]
36. Madison BB, Dunbar L, Qiao XT, Braunstein K, Braunstein E, Gumucio DL. Cis elements of the villin gene control expression in restricted domains of the vertical (crypt) and horizontal (duodenum, cecum) axes of the intestine. *J Biol Chem*. 2002; 277:33275–33283. [PubMed: 12065599]
37. Wang Y, Deb DK, Zhang Z, Sun T, Liu W, Yoon D, Kong J, Chen Y, Chang A, Li YC. Vitamin D receptor signaling in podocytes protects against diabetic nephropathy. *J Am Soc Nephrol*. 2012; 23:1977–1986. [PubMed: 23123403]
38. Okayasu I, Hatakeyama S, Yamada M, Ohkusa T, Inagaki Y, Nakaya R. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. *Gastroenterology*. 1990; 98:694–702. [PubMed: 1688816]
39. te Velde AA, Verstege MI, Hommes DW. Critical appraisal of the current practice in murine TNBS-induced colitis. *Inflamm Bowel Dis*. 2006; 12:995–999. [PubMed: 17012970]
40. Powrie F. T cells in inflammatory bowel disease: protective and pathogenic roles. *Immunity*. 1995; 3:171–174. [PubMed: 7648390]

41. Ostanin DV, Bao J, Koboziev I, Gray L, Robinson-Jackson SA, Kosloski-Davidson M, Price VH, Grisham MB. T cell transfer model of chronic colitis: concepts, considerations, and tricks of the trade. *Am J Physiol Gastrointest Liver Physiol*. 2009; 296:G135–146. [PubMed: 19033538]
42. Kuhn R, Lohler J, Rennick D, Rajewsky K, Muller W. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell*. 1993; 75:263–274. [PubMed: 8402911]
43. Berg DJ, Davidson N, Kuhn R, Muller W, Menon S, Holland G, Thompson-Snipes L, Leach MW, Rennick D. Enterocolitis and colon cancer in interleukin-10-deficient mice are associated with aberrant cytokine production and CD4(+) TH1-like responses. *J Clin Invest*. 1996; 98:1010–1020. [PubMed: 8770874]
44. Chen Y, Liu W, Sun T, Huang Y, Wang Y, Deb DK, Yoon D, Kong J, Thadhani R, Li YC. 1,25-Dihydroxyvitamin D Promotes Negative Feedback Regulation of TLR Signaling via Targeting MicroRNA-155-SOCS1 in Macrophages. *J Immunol*. 2013; 190:3687–3695. [PubMed: 23436936]
45. Qiu W, Wu B, Wang X, Buchanan ME, Regueiro MD, Hartman DJ, Schoen RE, Yu J, Zhang L. PUMA-mediated intestinal epithelial apoptosis contributes to ulcerative colitis in humans and mice. *J Clin Invest*. 2011; 121:1722–1732. [PubMed: 21490394]
46. Yu J, Zhang L. PUMA, a potent killer with or without p53. *Oncogene*. 2009; 27:S71–S83. [PubMed: 19641508]
47. Wang P, Qiu W, Dudgeon C, Liu H, Huang C, Zambetti GP, Yu J, Zhang L. PUMA is directly activated by NF-kappaB and contributes to TNF-alpha-induced apoptosis. *Cell Death Differ*. 2009; 16:1192–1202. [PubMed: 19444283]
48. Chen Y, Kong J, Sun T, Li G, Szeto FL, Liu W, Deb DK, Wang Y, Zhao Q, Thadhani R, Li YC. 1,25-Dihydroxyvitamin D(3) suppresses inflammation-induced expression of plasminogen activator inhibitor-1 by blocking nuclear factor-kappaB activation. *Arch Biochem Biophys*. 2011; 507:241–247. [PubMed: 21176770]
49. Chen Y, Du J, Zhang Z, Liu T, Shi Y, Ge X, Li YC. MicroRNA-346 mediates tumor necrosis factor alpha-induced downregulation of gut epithelial vitamin D receptor in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2014; 20:1910–1918. [PubMed: 25192497]
50. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005; 353:2462–2476. [PubMed: 16339095]
51. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007; 132:52–65. [PubMed: 17241859]
52. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004; 116:281–297. [PubMed: 14744438]
53. Zamore PD, Haley B. Ribo-gnome: the big world of small RNAs. *Science*. 2005; 309:1519–1524. [PubMed: 16141061]
54. Mohri T, Nakajima M, Takagi S, Komagata S, Yokoi T. MicroRNA regulates human vitamin D receptor. *Int J Cancer*. 2009; 125:1328–1333. [PubMed: 19437538]
55. Zella LA, Kim S, Shevde NK, Pike JW. Enhancers located within two introns of the vitamin D receptor gene mediate transcriptional autoregulation by 1,25-dihydroxyvitamin D3. *Mol Endocrinol*. 2006; 20:1231–1247. [PubMed: 16497728]
56. Zasloff M. Antimicrobial peptides in health and disease. *N Engl J Med*. 2002; 347:1199–1200. [PubMed: 12374882]
57. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. *FASEB J*. 2005; 19:1067–1077. [PubMed: 15985530]
58. Wang TT, Dabbas B, Laperriere D, Bitton AJ, Soualhine H, Tavera-Mendoza LE, Dionne S, Servant MJ, Bitton A, Seidman EG, Mader S, Behr MA, White JH. Direct and indirect induction by 1,25-dihydroxyvitamin D3 of the NOD2/CARD15-defensin beta2 innate immune pathway defective in Crohn disease. *J Biol Chem*. 2010; 285:2227–2231. [PubMed: 19948723]

59. Yuk JM, Shin DM, Lee HM, Yang CS, Jin HS, Kim KK, Lee ZW, Lee SH, Kim JM, Jo EK. Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. *Cell Host Microbe*. 2009; 6:231–243. [PubMed: 19748465]
60. Fritz T, Niederreiter L, Adolph T, Blumberg RS, Kaser A. Crohn's disease: NOD2, autophagy and ER stress converge. *Gut*. 2011; 60:1580–1588. [PubMed: 21252204]
61. Stappenbeck TS, Rioux JD, Mizoguchi A, Saitoh T, Huett A, Darfeuille-Michaud A, Wileman T, Mizushima N, Carding S, Akira S, Parkes M, Xavier RJ. Crohn disease: a current perspective on genetics, autophagy and immunity. *Autophagy*. 2011; 7:355–374. [PubMed: 20729636]
62. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol*. 2008; 8:685–698. [PubMed: 19172691]
63. Hart PH, Gorman S, Finlay-Jones JJ. Modulation of the immune system by UV radiation: more than just the effects of vitamin D? *Nat Rev Immunol*. 2011; 11:584–596. [PubMed: 21852793]

Highlights

- Intestinal epithelial VDR inhibits colitis by protecting the mucosal barrier
- Intestinal epithelial VDR levels are reduced in patients with IBD
- Intestinal epithelial VDR is down-regulated by a microRNA-mediated mechanism
- VDR is a key molecule in a regulatory circuit controlling mucosal inflammation
- Increasing gut epithelial VDR levels is a valuable strategy for IBD treatment

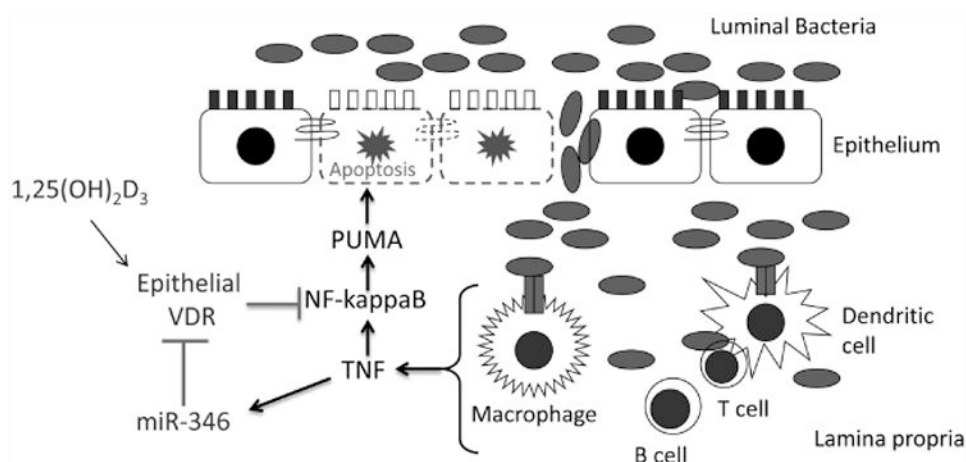


Figure 1.

Epithelial VDR is a key player in a mucosal regulatory circuit. Whereas VDR signaling maintains the integrity of the mucosal barrier by inhibiting inflammation-induced IEC apoptosis, VDR itself is down-regulated by mucosal inflammation. Thus increasing epithelial VDR levels might be valuable therapeutic strategy for the management of IBD. The cells illustrated here represent the major cell types that participate in the process of colonic inflammation.