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The role of UVR and vitamin D on T cells and inflammatory bowel disease

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Abstract

Vitamin D deficiency is associated with the development of inflammatory bowel disease (IBD). In experimental IBD the targets of vitamin D that result in protection from IBD include gut epithelial cells, innate immune cells, T cells and the microbiota. Ultraviolet radiation (UVR) induces production of vitamin D in the skin and suppresses T cell responses in the host. There is limited data demonstrating an effect of UVR on experimental IBD but the mechanisms of UVR suppression in IBD have not been defined. There are several shared effects of vitamin D and UVR on T cells including inhibition of proliferation and suppression of IFN-γ and IL-17 producing T cells. Conversely UVR decreases and vitamin D increases IL-4 production from T cells. Together the data suggest that UVR suppression of T cells and potentially IBD are both vitamin D dependent and independent.

Inflammatory Bowel Disease (IBD)

IBD are chronic diseases of the gastrointestinal tract of unknown etiology. In the United States, 1–1.3 million people have IBD and in Europe the incidence of IBD diseases are even higher than in the US.[1] Treating IBD can be a substantial economic burden; in the US the direct cost of living with IBD averages from $5,000–8,000 per year.[2] Ulcerative colitis and Crohn's disease make up two distinct forms of IBD. Ulcerative colitis is characterized by inflammation of the lower gastrointestinal tract from the colon to the rectum. Conversely, Crohn's disease is characterized by inflammation from the esophagus to the rectum, but most commonly occurs in the ileum of the small intestine. In Crohn's disease inflammation can affect all layers of the intestinal wall, not just mucosal layers.[3] For both diseases the immune system is inappropriately activated by the microbes found in the gut. Patients that develop IBD develop persistent inflammation that fails to resolve. Crohn's disease and ulcerative colitis have shared and distinct risk factors, as well as differences in treatments that point to both shared and unique pathophysiologies. For both Crohn's disease and ulcerative colitis there are genetic and environmental factors that determine which people develop disease.

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IBD is more common among biological relatives, and about 20% of patients (Crohn's and Colitis Foundation of America, http://www.ccfa.org/) have a relative with IBD, demonstrating the role of genetics in IBD. Several IBD susceptibility genes have been identified.[4] Single nucleotide polymorphisms in the major histocompatibility complex are linked to the development of many different immune-mediated diseases including IBD.[5] Major histocompatibility genes determine the targets of the immune system since they allow the immune system to identify pathogens but tolerate commensal microbes. IBD patients have genetic polymorphisms in multiple genes that control the immune response including several cytokines and cytokine receptor genes.[5–7] Other genetic polymorphisms exist in IBD patients for receptors that sense pathogens or are pattern recognition receptors like nucleotide oligomerization domain 2.[8] Mutations in nucleotide oligomerization domain 2 has been identified as a critical risk factor in Crohn's disease.[9, 10] Several of the genes linked to IBD susceptibility are important in the regulation of the immune response to microbes.

Identical twin studies have established an important role of the environment in the development of IBD. The concordance rate for ulcerative colitis in identical twins is only 20% and 50% in Crohn's disease.[11] In addition, the prevalence of IBD world wide has increased and even countries that previously had a low incidence of IBD have seen increases.[12] The incidence of IBD is higher in industrialized countries and in the northern hemisphere, IBD is more prevalent in northern versus southern climates. Environmental factors that may be different in low versus high IBD areas include diet, life-style, pollution, and sunlight (ultraviolet radiation, UVR). One environmental factor that is controlled by changes in diet and life-style are the commensal microbiota that inhabit the gastrointestinal tract. IBD patients have dysbiosis of the microbiota and the diversity of the microbiota is less as compared to healthy controls.[13] Environmental factors that contribute to the development of IBD have been difficult to identify but include the composition of the commensal microbiota, diet, vitamin D and sunlight. Here we will examine the specific role of UVR and vitamin D on IBD.

UVR and IBD

There are only a few studies that have analyzed the effects of UVR on IBD. These studies have been complicated by the fact that UVR exposure of skin results in the production of vitamin D. Vitamin D is produced by UVB radiation of the precursor 7-dehydrocholesterol in the skin to form pre-vitamin D, which is isomerized to vitamin D by heat.[14] Vitamin D from either the diet or UVR is first hydroxylated at the 25-position to produce 25hydroxyvitamin D (25,(OH)D) and then by the 1alpha hydroxylase to form active vitamin D or 1,25dihydroxyvitamin D ($1,25(OH)_2D$). There are two sources of vitamin D for production of $1,25(OH)_2D$, the diet and UVR light.

Incidence of immune-mediated diseases, including IBD, has been correlated with low sun exposure and latitude. The incidence of ulcerative colitis was 40% higher and Crohn's disease was 80% higher in northern Europe compared to southern Europe.[15] Other studies in France and Scotland showed similar results.[16] In France a study described a clear north-south gradient for the incidence of Crohn's disease, but not ulcerative colitis.[17] This same group later found a correlation between lower UVR exposure and the increased Crohn's

disease incidence observed in their earlier study.[17, 18] In the US, areas with lower UV exposure, had increased incidence of IBD, increased hospitalizations rates and increased severity of disease.[19–21] UV exposure was also associated with the risk of gastrointestinal *Clostridium difficile* infection.[22] In addition, patients with high UV exposure (Arizona), were 16% less likely to die from *C. difficile* infection in the hospital than patients with low UV exposure (Michigan), even when controlling for age, gender, and comorbidities.[22] The above studies did not include vitamin D measurements but did suggest that changes in vitamin D status might account for the effects of UVR on IBD incidence and severity.

Vitamin D and IBD

The vitamin D hypothesis suggests that vitamin D status is one of the environmental factors predisposing for the development of IBD.[23] The effect of UVR on vitamin D status depends on skin color, latitude, skin exposure, season etc. and therefore it has been difficult to determine the UVR contributions to vitamin D status. In addition there are important inter-personal variations in the effect of UVB light on 25(OH)D levels even when controlling for skin color.[24] Studies that use dietary intakes to estimate vitamin D status usually ignore any contributions from UVR. Even if 25(OH)D levels are measured it is difficult to determine how much comes from UVR versus diet and/or supplements. A recent systematic review and meta-analysis was done to determine the association of 25(OH)D levels, UVR exposure, geography and IBD.[25] The conclusions of the study were that both Crohn's disease and ulcerative colitis patients had lower levels of vitamin D and lower levels of 25(OH)D were associated with higher Crohn's disease activity indexes (CDAI; there were too few studies to evaluate ulcerative colitis).[25] However, because of a lack of adequate data no correlations could be made between latitude, geography and IBD.[25]

The data linking vitamin D and the propensity to develop IBD have been done without accounting for the possible contributions of UV light to the vitamin D status. The data so far demonstrating an inverse correlation between vitamin D status and IBD severity are stronger for patients with Crohn's disease than for patients with ulcerative colitis.[26] A prospective study that utilized the Nurses Health study and determined the relationship between 25(OH)D status and the risk of developing IBD showed a significant inverse risk between 25(OH)D levels and Crohn's disease but an insignificant inverse association for ulcerative colitis.[27] In two different prospective studies in Crohn's disease, patients with low 25(OH)D levels (<30ng/ml) required more hospitalizations and surgery compared to patients with higher 25(OH)D levels at entry.[28, 29] One of the two prospective studies included ulcerative colitis patients and showed that low 25(OH)D levels (<30ng/ml) resulted in more morbidity and treatment escalation over the 5 years of the study follow up for ulcerative colitis as well as Crohn's disease.[29] Crohn's disease patients in clinical remission had higher 25(OH)D levels than those with mild or moderate disease, and patients who used vitamin D supplements had lower C-reactive protein ($P=0.07$) and CDAI scores ($P<0.05$) than those who did not take supplements.[30] The stronger associations of vitamin D on Crohn's disease versus ulcerative colitis could be because of the differences in the etiology of the diseases as evidenced by the unique as well as shared genetic risk factors for the two diseases.[31] Vitamin D status is strongly inversely associated with IBD and especially Crohn's disease.

There have only been a few clinical interventions done using vitamin D supplementation of Crohn's disease patients. In a small open label pilot study, vitamin D supplementation for 6 months (5000 IU/d) improved quality of life scores in Crohn's subjects with mild to moderate disease, and most of the patients (78%) had CDAI scores below 150 indicating clinical remission after the 6 month intervention.[32] A second small open label study demonstrated a positive effect of vitamin D analog intervention (6 week treatment using 1alpha hydroxy-vitamin D) on CDAI scores.[33] Another small, double-blind randomized controlled study demonstrated an insignificant (P=0.056) decrease in relapse rate with the 12 month vitamin D intervention (1200 IU/d) as compared to placebo.[34] Each of the three vitamin D interventions in Crohn's disease utilized different vitamin D interventions and different study designs.[32–34] There is currently disagreement by the experts as to the effective dose, frequency of vitamin D delivery and serum 25(OH)D status cut offs for health outcomes; making it more difficult to determine the effects of vitamin D supplementation in clinical studies (reviewed in[26]). The results from the vitamin D interventions in Crohn's disease patients, while promising, require additional studies.

Vitamin D, UVR and experimental IBD

Mouse models of IBD have been useful for identifying novel therapeutics. There are many experimental models of IBD, and while no model perfectly represents human disease, these models are important in understanding mechanisms of IBD development. A comprehensive review of animal models of experimental IBD has been published by others.[35] Experimental IBD models fall into three categories: genetic models, transfer models, or chemical-induced injury models. Genetic manipulation to inhibit regulatory immune responses are common in IBD models, such as IL-10 KO.[35] IL-10 KO animals develop spontaneous colitis as a result of the lack of regulatory T (T reg) cells that produce most of the IL-10 in the gastrointestinal tract.[35] Transfer of naïve T cells to immunodeficient (no T or B cells) mice is an IBD model that has identified IFN-γ producing Th1 and IL-17 producing Th17 cells as the immunopathologic T cells in experimental IBD.[35] Co-transfer of naïve T cells with T reg cells that produce IL-10 eliminates disease by suppressing the production of IFN-γ and IL-17 by the naïve T cells in the immunodeficient recipients.[35] Chemical injury models of IBD have identified the important contribution of pattern recognition receptors of the innate immune system as important contributors to IBD susceptibility.[35] All of the experimental IBD models are affected by the commensal microbiota in the animal colonies. In dextran sodium sulfate induced colitis the microbes protect from gastrointestinal injury, while in other models (T cell transfer, IL-10 KO) the T cell response is generated against the microbes in the gastrointestinal tract.[35] The experimental IBD models have identified T cells, innate cells and the microbiota as key factors that regulate inflammation and disease in the gastrointestinal tract.

The effects of vitamin D on experimental IBD models have been reviewed.[36] Vitamin D deficient and VDR KO mice develop fulminating forms of several different models of experimental IBD.[36] Treating mice with the active form of vitamin D ($1,25(OH)_2D$) inhibited IBD in murine models of disease.[36] The targets of vitamin D in experimental IBD include gastrointestinal epithelial cell barrier function and both the innate and adaptive immune system.[36] More recently it has become clear that vitamin D alters the composition

of the commensal microbiota probably through regulation of the immune system.[36] The mechanisms by which vitamin D regulates experimental IBD include regulation of gut barrier function, the microbiota and the immune system to maintain gastrointestinal homeostasis.

Two studies have examined the effects of UVR in one model of experimental IBD. The model that was tested is acute dextran sodium sulfate colitis in mice. Colitis in this model is a result of injury in the gastrointestinal tract that is then repaired by the innate immune system, without a contribution of T cells.[35] The experimental design for both studies was similar in that the light therapy was delivered before induction of colitis.[37, 38] Both studies showed a positive effect of the light treatments on experimental IBD symptoms in this model.[37, 38] The dose of light was sufficient in one study to raise serum 25(OH)D levels but in the other was not.[37, 38] The doses of light delivered were 600mJ/cm^2 (no raise in serum 25(OH)D) on shaved mice versus 14 J/cm^2 on unshaved mice (raised serum 25(OH)D).[37, 38] The low dose (600mJ/cm^2) was associated with an increase in T reg cells.[38] However T reg cells have not been shown to be important in this model of chemically induced colitis. The data suggest that there may be a vitamin D independent effect of UVR on experimental colitis.[37, 38] Future work should focus on the effects of UVR in other experimental models of IBD that involve T cells and the utilization of VDR KO mice to determine the UVR induced versus the vitamin D mediated effects of UVR treatments.

Vitamin D/UVR regulation of T cells

While it is clear that innate immune cells, the microbiota, the gut epithelium and T cells are critical regulators of gastrointestinal homeostasis, this commentary will focus on the effects of vitamin D versus UVR on T cells. Dysregulation of T cells leads to IBD and 1,25(OH)$_2$D and UVR have effects on T cells. Vitamin D is a critical factor in the development and function of T cells. The targets of vitamin D in T cells include inhibition of proliferation of T cells and 1,25(OH)$_2$D mediated inhibition of T cell produced IL-17 and IFN-γ (Fig. 1).[39–41] UVR also results in the inhibition of T cell proliferation and a more global inhibition of T cell produced Th1, Th17 and Th2 (IL-4 secreting T cells) cytokine responses in effector T cells (Fig. 1).[42] The immunosuppression following UVR exposure and 1,25(OH)$_2$D is acute in that antigen sensitization immediately following UVR/1,25(OH)$_2$D exposure is affected but subsequent exposures to new antigens are not affected.[23, 41, 42] The induction of FoxP3$^+$ T reg cells by 1,25(OH)$_2$D and UVR is also an overlapping function of the two treatments (Fig. 1).[38–40, 42] 1,25(OH)$_2$D and UVR increased production of IL-10 by T cells (Fig. 1). Common functions of UVR and 1,25(OH)$_2$D treatments include suppression of T cell proliferation, inhibition of Th1/Th17 effector cells and induction of T reg cells and IL-10 production (Fig. 1).[23, 41, 42]

Vitamin D is critical in the development of invariant (i) natural killer (NK)T cells and CD8αα T cells. iNKT cells are T cells that respond to lipid antigens and rapidly produce cytokines. iNKT cells have been shown to be important regulators of experimental IBD (dextran sodium sulfate induced colitis).[43] The gastrointestinal tract harbors a unique T cell population that express CD8αα.[44] The CD8αα receptor on these T cells helps to maintain tolerance to the large number of microbial and food antigens found in the gut.[44] VDR KO

have fewer iNKT cells and CD8αα compared to WT mice, and the CD8αα T cells from the gut of the VDR KO produced less IL-10 (Fig. 1).[45, 46] Vitamin D status and expression of the VDR are required for the normal development of iNKT cells and CD8αα T cells that regulate experimental IBD (Fig. 1).[45, 46] Reduced iNKT cell or CD8αα T cell functions results in poorly controlled Th1 and Th17 cell responses in the gut (Fig. 1). $1,25(OH)_2D$ inhibited IL-17 and induced IL-10 production from iNKT cells.[46] There is one study that has looked at the effects of UVR on NKT cells and shown that UVR induces NKT cells that suppress antigen specific responses.[47] The UVR NKT cells were CD1d restricted and showed increased IL-4 production with UVR treatment but may be distinct from the iNKT cells that have been the focus of the vitamin D work.[46, 47] Additional work is needed to determine whether the effects of UVR on NKT cells is via the production of $1,25(OH)_2D$ and induction of iNKT cells (Fig. 1). The targets of vitamin D in T cells, includes regulation of iNKT cell and CD8αα T cell development and function (Fig. 1).

The mechanisms by which UVR regulate T cells directly in the absence of induction of vitamin D production have not been well studied. The UVR effects cannot be reproduced *in vitro* which complicates clear determinations of vitamin D versus UVR mediated effects. The effects of UVR on T cells includes inhibition of T cell proliferation and suppression of all antigen specific responses including Th1, Th17 and Th2 (Fig. 1).[42, 48] $1,25(OH)_2D$ treatment of T cells induced IL-4 production from Th2 cells.[41] Mechanisms whereby UVR could regulate the T cell is via prostaglandin-E2 production and the formation of pyrimidine dimers and urocanic acid production.[49, 50] These UVR induced factors have been shown to induce T reg cells and IL-10 production following UVR exposure of skin.[49, 50] UVR was shown to induce functional T regs in VDR KO mice.[51] Independent of vitamin D, UVR induced T regs and suppressed antigen specific immune responses in vivo.[51] The factors that mediate regulation of T cells following UVR exposure include both vitamin D independent and dependent effects of UVR (Fig. 1).

Conclusions

UVR and vitamin D are two related environmental factors that have been hypothesized to be etiological factors important in the development of IBD. At present there is strong evidence associating vitamin D status as a risk factor for IBD, especially Crohn's disease. The evidence for geography, latitude or UVR exposure and IBD does not exist. Animal models have been useful for identifying the targets of vitamin D in experimental IBD, which include T cells, innate immune cells, epithelial cells and the microbiota. A more limited number of studies (two) have studied UVR and experimental IBD without identifying the specific targets in this model. UVR is an effective inhibitor of antigen specific T cell responses. UVR and $1,25(OH)_2D$ have some shared as well as unique effects on T cells. Overall the data support UVR effects on T cells (and potentially IBD) that are both vitamin D dependent and vitamin D independent. IBD patients might be the ideal population for the utilization of UVR therapy. Because of the malabsorption associated with the IBD diseases oral vitamin D supplementation can be ineffective. UVR might increase vitamin D status and have other non-vitamin D mediated benefits in this population.

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Biographies

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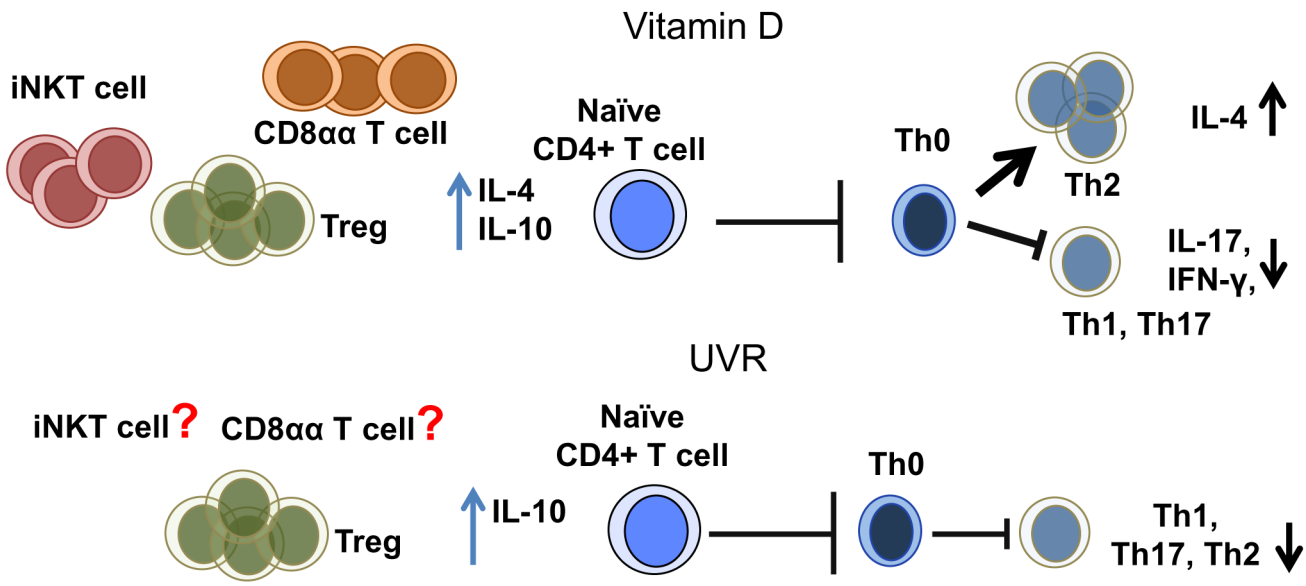

Figure 1. Vitamin D versus UVR effects on T cells

The shared effects of both vitamin D and UVR on T cells includes induction of IL-10 producing T regs and suppression of T cell proliferation and Th1 and Th17 cells that produce IL-17 or IFN-γ. UVR suppresses induction of Th2 cells, while $1,25(OH)_2D$ induces IL-4 production from Th2 cells and iNKT cells. In addition, vitamin D is a critical factor in the development of iNKT cells and CD8αα T cells that help to maintain tolerance in the gastrointestinal tract. It is presently unclear what the effects of UVR are on either iNKT cells or CD8αα T cells.