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Vitamin D, Multiple Sclerosis and Inflammatory Bowel Disease

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Abstract

It has now been more than 20 years since the vitamin D receptor was identified in cells of the immune system. The immune system has now been established as an important target of vitamin D. Vitamin D receptor knockout and vitamin D deficient mice have a surplus of effector T cells that have been implicated in the pathology of multiple sclerosis (MS) and inflammatory bowel disease (IBD). The active form of vitamin D directly and indirectly suppresses the function of these pathogenic T cells while inducing several regulatory T cells that suppress MS and IBD development. There is reason to believe that vitamin D could be an environmental factor that may play a role in the development of these immune mediated diseases in the clinic but at present there has not been a causal relationship established. Nonetheless, current evidence suggests that improving vitamin D status and/or using vitamin D receptor agonists may be useful in MS and IBD.

The incidences of immune mediated diseases like multiple sclerosis (MS) and inflammatory bowel diseases (IBD) have increased in developed countries over the last 50 years. To explain the increased incidence of immune mediated diseases as well as the geographical restriction of these diseases to the developed world the hygiene and vitamin D hypotheses have been put forward [1, 2]. The hygiene hypothesis states that reduced exposure to microbial components results in immune-dysregulation and T cell responses that drive immune mediated disease. The vitamin D hypothesis proposes that vitamin D regulates the development and function of the immune system and that changes in vitamin D status especially prenatal as well as childhood alterations affect the development of the resultant immune response and the development of diseases like IBD and MS. It is likely that there are multiple genetic and environmental factors that determine susceptibility to MS and IBD but here the role that vitamin D plays in the regulation of these two immune mediated diseases will be reviewed.

Animal models of IBD and MS

Animal models of autoimmune diseases have been useful for identifying the mechanisms that lead to disease development, testing therapeutic modalities and understanding how therapies or nutritional interventions function. Interferon (IFN)-γ and interleukin (IL)-2 are produced by type-1 helper T cells (Th1) and these cells have been shown to be important in

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the generation of cell mediated immune responses including host protection from intracellular infections and tumors. Th1 cells are not always protective and in IBD and MS Th1 cells are pathogenic effector cells. More recently a second Th cell subset has been described as pathogenic in IBD and MS, the Th17 cells. Regulation of these two cell types effectively suppresses development of both IBD and MS. Much of what is known about the mechanisms underlying induction and regulation of Th1 and Th17 cells has been generated in animal models of IBD and MS.

There are two types of animal models of MS those that are autoimmune and those that develop following a viral infection [3]. The best studied model of MS is experimental autoimmune encephalomyelitis (EAE) that develops following immunization of susceptible strains of mice and rats with central nervous system (CNS) proteins in complete Freund's adjuvant and injections of Pertussis toxin [3]. EAE has been extremely useful for understanding how pathogenic T cells are activated and cause disease in the CNS [3]. In order for EAE symptoms to occur, T cells that produce Th1 and Th17 cytokines must be induced to target the CNS [4, 5]. In addition, the T cells need to cross the blood brain barrier and enter the immune-privileged site. Conversely, regulatory T cells (Treg) especially the FoxP3 expressing T cells and a shift to a Th2 response are associated with reduced symptoms of EAE [6]. The viral models of MS are useful for studying disability and demyelination since the viruses are neurotropic and target the CNS in mice [3]. No model of MS is ideal since only some aspects of the human disease are reproduced, but EAE in particular has been a valuable model to study T cell subsets that induce and/or resolve paralysis symptoms in animals.

There are several different experimental animal models of IBD. IL-2 KO and IL-10 KO mice have defective T reg cells and as a result IBD symptoms develop spontaneously in these mice [7]. The gut microbial flora is important in experimental IBD since the alterations in the types and amounts of organisms present has been shown to determine how quickly inflammation and IBD develop in IL-10 KO mice [7, 8]. Chemical injury of the gastrointestinal tract following treatment with dextran sodium sulfate (DSS) or trinitrobenzene sulfonic acid (TNBS) induces experimental IBD. In the DSS model short-term DSS treatment results in compromised barrier function followed by acute inflammation, recovery and healing of the gut mucosa. TNBS colitis symptoms are due to over production of IL-17 and IFN-γ. Naïve T cells transferred into recombinase activator gene (Rag) knockout (KO) mice become Th17 cells and IBD symptoms develop in recipient mice [9]. Th1 and Th17 cells are pathogenic in IL-10 KO, TNBS, Rag KO transfer and infection induced experimental IBD models [9–11]. Conversely, a failure to produce enough regulatory T cells (IL-10 KO and IL-2 KO) also results in IBD. Host genetic effects (T reg dysfunction), microflora disruption or infection and induction of polarized Th1 and Th17 cells all result in experimental IBD.

Experiments in animal models of IBD and MS have allowed for the identification and testing of the causes and potential cures for these complex diseases. The models indicate that several common factors affect the development of both experimental IBD and EAE. Experimental IBD and EAE are both more severe when there are many Th1 and Th17 cells and few regulatory T cells that normally inhibit and shut off the Th1 and Th17 cells. No one animal model replicates these complex and heterogeneous family of diseases, but the animal models have been extremely valuable for identifying mechanisms that lead to disease and potential novel therapies.

Environment and IBD/MS

Autoimmunity develops because of the interaction between genes and environment. The expression of several genes have been associated with the increased likelihood of developing autoimmunity [12]. Genes important in the generation of autoimmunity include cytokines, pattern recognition receptors, and major histocompatability complex genes [12, 13]. Identical twin studies clearly show that inheriting an autoimmune genotype is not enough to develop autoimmunity, since the IBD and MS concordance rates for identical twins is only 14% for ulcerative colitis, 30% for MS and 50% for Crohn's disease [13, 14]. It has long been appreciated that the environment has an important impact on the development of autoimmune disease. The mechanisms by which the environment is affecting the development of autoimmunity are beginning to be appreciated with the identification of several different pathways that result in epigenetic modification of gene expression. However, it continues to be difficult to systematically identify the environmental factors important in the development of IBD and MS. IBD and MS are more prevalent in the developed versus undeveloped countries. Along the equator IBD and MS are almost non-existent [15, 16]. The hygiene hypothesis proposes that the high rates of infection in the developing world and especially helminth infections program the immune system in a way that precludes autoimmunity. Experimentally it has been shown that infection and commensal bacteria were critical in the development of experimental animal models of both IBD and MS [17–19]. Furthermore helminth infections can protect mice from experimental IBD [20]. Germfree animals failed to develop several different models of IBD [18, 19]. Not all infections were protective against IBD and MS as some infections were associated with increased autoimmunity. *Mycobacteria* infections were associated with IBD development and Ebstein-Barr virus may play a role in MS disease development [21, 22]. There is evidence to suggest that the commensal bacterial flora and other infections are environmental influences on the development of IBD and MS.

The vitamin D hypothesis could also be used to explain the higher incidence of IBD and MS in developed versus undeveloped countries. Developing countries are generally found in closer proximity to the equator where sunlight exposure and vitamin D would be produced from the skin at higher levels. In addition, IBD and MS are most prevalent in the northern parts of the US and all parts of Canada compared to the southern parts of the US [23]. The findings of a recent meta-analysis show that latitude is associated with the development of MS [24]. The latitude effect could be because of the documented immunosuppressive effect of UVB light on immunity and/or production of vitamin D. Recently it has been shown that UVB light suppresses EAE independent of any effect on 25(OH)D3 status [25]. That data would suggest a sunlight effect on MS independent of vitamin D. Bone disease, low vitamin D intakes and low 25(OH)D3 status have been associated with increased incidence of IBD and MS [26–29]. There have been some vitamin D interventions that show benefits but there have not been randomized double blind controlled studies that establish cause and effect [26, 30].

Vitamin D and T cells

In 1983 it was first described that immune cells had vitamin D receptors (VDR) [31, 32]. Currently what is known is that all cells of the immune system can express the VDR and that activation results in upregulation of the VDR [33, 34]. Induction of the VDR following activation suggests that resting cells may not respond to 1,25dihyroxyvitamin D3 (1,25D3) until they are activated. The early experiments used human peripheral blood mononuclear cells treated with 1,25D3 and mitogens that polyclonally activated T cells in the cultures [35–37]. What was found was that the 1,25D3 treated T cells proliferated less and made less IFN-γ and IL-2 than controls [35–37]. Furthermore, 1,25D3 inhibited both Th17 and Th1

cell function [38–41]. The effects of 1,25D3 on Th17 and Th1 cells has been shown to be due to direct effects on IFN-γ and IL-17 production but also indirect effects of 1,25D3 on dendritic cells and macrophages [38]. In addition, 1,25D3 induced the development of regulatory T cells (T reg) that were protective against autoimmunity [41, 42]. Other regulatory cells including iNKT cells and a specialized population of T cells in the gut that express CD8$\alpha\alpha$ are vitamin D targets [43, 44]. The effects of vitamin D and 1,25D3 on T cells predicts that autoimmune diseases like MS and IBD might be responsive to 1,25D3.

Vitamin D and experimental IBD

Several different models of experimental IBD have been used to examine the effect of changes in vitamin D status and/or treatment with 1,25D3 agonists on disease severity (Table 1). Vitamin D deficiency has been shown to accelerate the development of IBD symptoms in IL-10 KO mice [45]. In addition, double VDR and IL-10 KO mice developed a fulminating form of IBD that resulted in ulceration of the intestine and the premature mortality of the mice within a very short time frame (3–5 wks of age, [46]). VDR KO mice did show microscopic lesions in the gut including increased amounts of inflammatory cytokines as they aged; however, the VDR KO mice did not spontaneously develop overt symptoms of IBD [47]. When treated with DSS, VDR KO mice developed a lethal form of colitis [48]. Naïve VDR KO T cells were found to transfer a more severe form of IBD to T and B cell deficient (RAG KO) than naïve wildtype (WT) T cell transfer [46]. 1,25D3 and analogs of 1,25D3 have been shown to suppress IBD in the IL-10 KO mice, and in chemical injury models [45, 48, 49]. The effects of 1,25D3 in the IL-10 KO mice required adequate dietary calcium, suggesting that 1,25D3 may directly and indirectly, through calcium regulation, control immune function in vivo [50]. Evidence from multiple different models suggests that vitamin D and VDR deficiency result in the increased susceptibility of mice to experimental IBD. In addition, 1,25D3 suppressed experimental IBD symptoms [45, 48].

Vitamin D and EAE

1,25D3 treatment has been shown to suppress EAE by multiple different investigators [51–56]. The effectiveness of 1,25D3 to suppress EAE required adequate dietary calcium [57]. In addition, elevated serum calcium in the absence of 1,25D3 treatment or the ability to produce 1,25D3 suppressed EAE [58]. These data point to a critical role for calcium, independent of 1,25D3, in the suppression of EAE. Originally removal of vitamin D from the diet decreased the time to first EAE symptom but only in female mice [51]. Surprisingly VDR KO mice were shown to be more resistant to EAE [55]. Recently two publications convincingly show that complete vitamin D deficiency is protective in mice with EAE [59, 60]. These data might be interpreted as evidence that there is not a connection between vitamin D status and MS. However, vitamin D deficiency results in a decreased effectiveness of T cell immunization for delayed type hypersensitivity responses [61]. Because of the need for immunization in the development of EAE it seems possible that a failure to adequately prime Th1 and Th17 cells in the vitamin D deficient host may be the cause for the lower susceptibility of vitamin D deficient mice to EAE. Further experimentation will be required to understand these seemingly paradoxical results.

Mechanisms of vitamin D influence on IBD and EAE

Comparing the effects of vitamin D status, VDR expression and 1,25D3 treatment on the models is helpful for understanding mechanisms and targets of vitamin D. Innate immune mechanisms including barrier function, macrophage and dendritic cells are vitamin D targets. Acute DSS colitis results because of chemical injury, breached mucosal barrier function and production of tumor necrosis factor (TNF)-α by macrophage. DSS colitis is suppressed by 1,25D3 and extremely severe in VDR KO mice (Table 1, [48]). Barrier

function has been shown to be diminished in the VDR KO mice and together with elevated TNF-α production by macrophage suggest that innate and adaptive immune responses are regulated by 1,25D3 and vitamin D [48].

Vitamin D has been shown to induce anti-bacterial peptides and alter the composition of the gut microbial flora [62]. Vitamin D and VDR deficiency in IL-10 KO mice results in a fulminating and accelerated form of the disease [45, 46]. VDR and IL-10 double KO (DKO) mice developed fulminating IBD even when treated with broad spectrum antibiotics that completely prevented the development of IBD in single IL-10 KO mice [44]. Even though IL-10 KO mice had defective T regs, 1,25D3 was suppressed IBD by inhibiting TNF-α production [50]. In IL-2 KO mice there was no effect of either 1,25D3 treatment or vitamin D deficiency, which suggests the production of IL-2 is critical to the effectiveness of vitamin D in this model (Table 1, [63]). T regs, the gut microflora, IL-2, IL-10 and TNF-α are all important vitamin D targets.

Th1 and Th17 are pathogenic cells in both experimental IBD and EAE. Naïve T cells transferred into Rag KO mice became Th17 cells that induced a T cell mediated model of IBD. Naïve T cells from VDR KO mice induced more severe IBD than their WT counterparts (Table 1, [46]). TNBS colitis is inhibited by 1,25D3 and the inhibition was a result of a shift from a Th1 and Th17 response to a Th2 and regulatory T cell (Treg) response (Table 1, [49]). The mechanisms by which 1,25D3 functions to suppress EAE include induction of regulatory T cells and suppression of Th1 and Th17 cells (Table 1, [52, 64]). IL-4 KO mice develop EAE symptoms but 1,25D3 failed to protect the mice from EAE, suggesting that production of IL-4 and induction of Th2 cells was critical to the function of 1,25D3 in this model (Table 1, [65]). In vivo, induction of Th2 cells by 1,25D3 was responsible for the beneficial effects in both EAE and IBD. In both the gut and the CNS; 1,25D3 suppressed the development and function of Th17 and Th1 cells. The further benefits of 1,25D3 included induction of Th2 cells and T regs that indirectly suppressed Th1 and Th17 cells.

VDR KO mice are useful for determining what the targets of vitamin D are in the immune system. VDR KO mice are predisposed to develop inflammation in the gut. Although there is a decreased incidence of EAE in the VDR KO mouse (Table 1, [55]), WT recipients of VDR KO bone marrow developed an aggressive form of EAE that was more severe than in WT mice [54]. The data from the bone marrow chimeras suggest that the immune compartment in the VDR KO mice was intact and gave rise to pathogenic Th1/Th17 cells. Analyses of the T cells in the VDR KO mice showed that CD4+ T cells were predisposed to become Th17 cells and that more activated/memory T cells accumulated in the VDR KO mice [38]. Naïve CD4+ T cells from VDR KO mice transferred more severe IBD because of the over production of Th1 and Th17 cells [38, 46]. In addition, VDR/Rag double KO mice rapidly induced naïve T cells that produced IL-17 and caused a fulminating form of disease compared to single Rag KO mice [38]. Regulatory cells in VDR KO mice were also defective [44]. However, the FoxP3+ T reg cells developed and functioned normally from VDR KO mice [44]. Instead there were defects in iNKT cell and CD8αα/TCRαβ T cells in the VDR KO mice [43, 44]. The CD8αα/TCRαβ T cells are critical in the maintenance of gastrointestinal homeostasis and iNKT cells are critical regulatory cells in both the CNS and gut. Data from the VDR KO mice showed a requirement for the VDR for normal T cell function.

Conclusions

Vitamin D is required for the normal development of murine T cells. In addition, 1,25D3 treatment suppressed the development of EAE, IBD and several other models where Th1

and Th17 cells were pathogenic. Vitamin D and 1,25D3 were critical for the development of regulatory cells including T reg, iNKT cells and CD8αα/TCRαβ T cells. In the absence of vitamin D the gastrointestinal tract was more susceptible to autoimmunity. The role of vitamin D status in the CNS is less certain but it may be that experimental limitations explain the reduced incidence of EAE in vitamin D deficient and VDR KO mice. There is evidence that vitamin D status and 1,25D3 may also regulate human T cell development, MS and IBD. Further research is needed to determine which of the vitamin D mediated effects occur in human cells and patients. Overall the available data do suggest that vitamin D status and 1,25D3 agonists would be useful for normalizing T cell function and in the prevention and treatment of human MS and IBD.

Abbreviations used

DSS	dextran sodium sulfate
D-	vitamin D deficient
EAE	experimental autoimmune encephalomyelitis
IBD	inflammatory bowel disease
MS	multiple sclerosis
IFN	interferon
IL	interleukin
KO	knockout
1,25D3	1,25dihydroxyvitamin D3
TNBS	trinitrobenzene sulfonic acid
TNF	tumor necrosis factor
VDR	vitamin D receptor
WT	wildtype

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Highlights

Vitamin D regulates experimental autoimmune disease.

1,25dihydroxyvitamin D regulates T cells directly and indirectly through calcium.

The immune system is an important vitamin D target.

Benefits for increasing vitamin D intakes in human autoimmunity are proposed but not proven.

Table 1

Effects of vitamin D status and 1,25D3 on EAE and experimental IBD.

Model IBD	Mechanism of disease[a]	1,25D3[b]	VDR/D−	Reference(s)
IL-10 KO	T reg deficiency/gut flora	↓	– –	[45, 46]
IL-2 KO	T reg deficiency	-	-	[63]
DSS	macrophage/barrier function	↓	–	[48]
TNBS	Th1/Th17	↓	ND	[49]
T cell transfer	naïve T cell/Th17	ND	–	[46]
EAE				
WT	Th1/Th17	↓	↓	[51–56, 59]
IL-4 KO	Th2 deficiency	-	ND	[65]

[a]Mechanisism by which either IBD or EAE develops.

[b]1,25D3: Effect of 1,25D3 or 1,25D3 agonists on disease development.

VDR/D-: Effect of VDR or vitamin D deficiency (D-) on disease development. ND: not done, -: no change in disease,↓- decreased disease, – – - increased severity of disease.