



Review

Vitamin D and its role in immunology: Multiple sclerosis, and inflammatory bowel disease

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Abstract

Autoimmune diseases like multiple sclerosis (MS) and inflammatory bowel disease (IBD) occur because of an inappropriate immune-mediated attack against self-tissue. Analyses of genetically identical twins shows that besides genetics there are important environmental factors that contribute to MS and IBD development. Vitamin D availability due to sunshine exposure or diet may play a role in the development of MS and IBD. Compelling data in mice show that vitamin D and signaling through the vitamin D receptor dictate the outcome of experimental MS and IBD. Furthermore, the evidence points to the direct and indirect regulation of T cell development and function by vitamin D. In the absence of vitamin D and signals delivered through the vitamin D receptor, auto reactive T cells develop and in the presence of active vitamin D ($1,25(\text{OH})_2\text{D}_3$) and a functional vitamin D receptor the balance in the T cell response is restored and autoimmunity avoided.

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1. Autoimmunity

The immune system has evolved to protect us from disease causing microorganisms. In order to do this the immune system must differentiate between things that belong (self) and things that do not belong (non-self).

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In some individuals there is a flaw in the process and autoimmune disease occurs as a consequence of the inappropriate reactivity to self. In autoimmune patients, T cells develop in the periphery that target tissues such as the central nervous system (multiple sclerosis), the gut (inflammatory bowel diseases), the joints (arthritis) and the pancreas (type-1 diabetes). The commonality between these diseases are that T-cells and in particular Th1 cells drive disease pathology. Th1-mediated autoimmune diseases are characterized by Th cells that secrete tumor necrosis factor (TNF)- α , and interferon (IFN)- γ that home to self-tissues and induce inflammation at those sites (inflammatory bowel disease (IBD)-gut, multiple sclerosis (MS)—central nervous system). In general, if a treatment for Th1-mediated autoimmunity works it suppresses the number of Th1 cells and/or the cytokines (TNF- α in particular) that they produce. In addition, treatments that work for one Th1 driven disease are likely to suppress other Th1 driven autoimmune diseases.

Autoimmune diseases are of unknown etiology. Complicated interactions between multiple genes and the environment dictate which individuals will develop any given autoimmune disease. Vitamin D may be an environmental factor that contributes to autoimmune disease development. Environmental sources of vitamin D include the diet and the production of vitamin D3 in the skin following UV exposure of the skin precursor seven-dehydrocholesterol (DeLuca, 1993). Vitamin D3 synthesis is a relatively efficient process in which 10 min of summer sun will produce the recommended daily intake for humans (400 IU, DeLuca, 1993). Dark skin, and the skin of the elderly are less efficient producers of vitamin D (Holick et al., 1981). Furthermore, sunscreen application blocks the UV wavelengths required for vitamin D3 synthesis. In addition, dietary intake of vitamin D is problematic since there are few foods, which are naturally rich in vitamin D. Here evidence will be provided in MS and IBD that suggests that vitamin D status available in the environment either following UV release of vitamin D in the skin or ingestion of vitamin D in the diet is a factor that contributes to both MS and IBD development.

2. Inflammatory bowel disease

IBD are immune-mediated diseases of unknown etiology affecting the gastrointestinal (GI) tract. There are at least two distinct forms of IBD, ulcerative colitis and Crohn's disease. IBD are chronic recurring illnesses most commonly involving inflammation of the terminal ileum and colon, although these diseases can also affect many sites throughout the alimentary tract. In North America and Europe about 1 in 1000 people are affected with IBD (Podolsky, 1991a, b). The effect of genes on disease develop is shown in biological relatives and siblings of IBD patients who are at an increased (10- and 40-fold higher, respectively) risk of developing IBD. However, monozygotic twins only have concordance rates of 50% (Crohn's) or less (18%, ulcerative colitis). Therefore 50% of the time or more genetically identical individuals do not both develop IBD. Vitamin D from sunlight exposure is less in areas where IBD occurs most often, as IBD is most prevalent in northern climates, such as North America and Northern Europe (Podolsky, 1991a, b; Sonnenberg et al., 1991). Vitamin D deficiency is common in patients with IBD even when the disease is in remission (Andreassen et al., 1997, 1998). It is unclear why vitamin D deficiency occurs more frequently in IBD. It is probably due to the combined effects of low vitamin D intake, malabsorption of many nutrients including vitamin D, and decreased outdoor activities in climates that are not optimal for vitamin D synthesis in the skin.

3. Multiple sclerosis

Multiple sclerosis afflicts 350,000 people in the US alone. Like IBD there is clear and compelling evidence for the environment in the etiology of disease. The concordance rate between monozygotic twins for MS is only 30%. That is, 70% of the time only one of the pair of genetically identical individuals develops disease. MS is a disease that is essentially unknown at the equator and the prevalence of the disease increases in populations that live farther away from the equator (Hayes, 2000). A recent, large epidemiological study showed that women with the highest vitamin D intakes (used supplements) had a 40% reduction in the risk of developing MS (Munger et al., 2004). Like IBD, vitamin D deficiency is common in patients with MS (Cantorna, 2000). The cause of low vitamin D levels in MS patients is also likely to be due to a combination of low vitamin intakes and decreased outdoor activities in climates that are not optimal for vitamin D synthesis in the skin.

4. Vitamin D and experimental autoimmunity

The classical function of vitamin D is in the regulation of calcium homeostasis and thus bone formation and resorption. The identification of vitamin D receptors (VDR) in peripheral blood mononuclear cells sparked the early interest in vitamin D as an immune system regulator (Bhalla et al., 1983; Provvedini et al., 1983). Vitamin D is a member of the steroid thyroid super family of nuclear receptors. Active vitamin D ($1,25(\text{OH})_2\text{D}_3$) functions by binding to the VDR. Together with a number of other transcription factors the $1,25(\text{OH})_2\text{D}_3$ /VDR complex regulates the transcription of genes which contain vitamin D response elements. All the members of the steroid hormone super family have been shown to regulate gene transcription.

In vivo the immune targets of vitamin D have been defined primarily in Th1 driven autoimmune diseases. Vitamin D deficiency accelerates the development of experimental MS, and type-1 diabetes (Cantorna et al., 1996, 1998, 2000; Zella and DeLuca, 2003). Conversely, $1,25(\text{OH})_2\text{D}_3$ treatment suppressed the development of these Th1-mediated autoimmune diseases (Cantorna et al., 1996, 1998, 2000; Zella and DeLuca, 2003). In addition, $1,25(\text{OH})_2\text{D}_3$ treatment of mice with ongoing MS symptoms halted the progression of the disease in these mice, showing that vitamin D altered the immune response even after the disease had been established (Cantorna et al., 1996). $1,25(\text{OH})_2\text{D}_3$ has been shown to inhibit Th1 driven responses in a number of different models.

Experimental IBD in the interleukin (IL)-10 KO mouse is a spontaneous disease, which develops in part due to an inappropriate response to the normal bacterial flora in the small intestine and large intestine of the mice. Experimental IBD is induced by TNF- α and IFN- γ secreting Th1 cells. Th2 or T regulatory cells inhibit both the development and function (cytokine secretion) of Th1 cells. Vitamin D sufficient chow fed IL-10 KO mice develop IBD beginning at 12 weeks of age. Vitamin D deficiency accelerated the development of symptoms in the IL-10 KO mice (Cantorna et al., 2000) such that 100% of the vitamin D deficient IL-10 KO mice had symptoms (diarrhea, rectal bleeding) of IBD and 60% died due to a severe form of IBD before 9 weeks of age (Cantorna et al., 2000; Froicu et al., 2003). In contrast vitamin D sufficient mice showed no outward symptoms of IBD in the same time frame (Cantorna et al., 2000; Froicu et al., 2003). Confirming the vitamin D deficiency data, mice that are both IL-10 and VDR deficient (double VDR/IL-10 KO) develop a fulminating form of experimental IBD that leads to 100% mortality by 7 weeks of age (Froicu et al., 2003). Interestingly the severity of IBD in the VDR/IL-10 KO mice is the same regardless of whether or not disease-causing microorganisms are present in the colony. Both vitamin D deficiency and VDR deficiency render experimental IBD more severe.

5. T cells are vitamin D targets

The VDR is present in multiple cells of the immune system and the targets of $1,25(\text{OH})_2\text{D}_3$ in these cells has begun to be explored. The presence of the VDR in both the thymus and the peripheral T cells suggests a role for vitamin D in both development and function of T cells. The regulation of T cells is a result of both direct and indirect actions of vitamin D (Adorini, 2002; Mahon et al., 2003). If vitamin D or signals through the VDR are limiting Th1 cells are favored at the expense of regulatory T cells and Th2 cells (Fig. 1, Cantorna and Mahon, 2004; Cantorna et al., 2004). $1,25(\text{OH})_2\text{D}_3$ increases regulatory T cells and IL-4 production by Th2 cells (Fig. 1, Adorini et al., 2003; Mahon et al., 2003). Physiologically the VDR is required to maintain a balance in the T cell response and furthermore in the absence of the VDR Th2 cells are diminished (Fig. 1, Froicu et al., 2003). More recent unpublished data suggests that T regulatory function may be compromised in the VDR KO mouse (Cantorna unpublished). Normal T cell function and the prevention of autoimmune disease require vitamin D and signaling via $1,25(\text{OH})_2\text{D}_3$ and the VDR.

6. Conclusions

A model is proposed whereby the amount of vitamin D in the environment (food and sunlight exposure) affects both the development and function of T cells and therefore the immune system. The experimental evidence suggests that autoimmune diseases like IBD and MS are acutely affected by changes in vitamin D status and VDR signaling. The implications are that genetically predisposed individuals that either do not

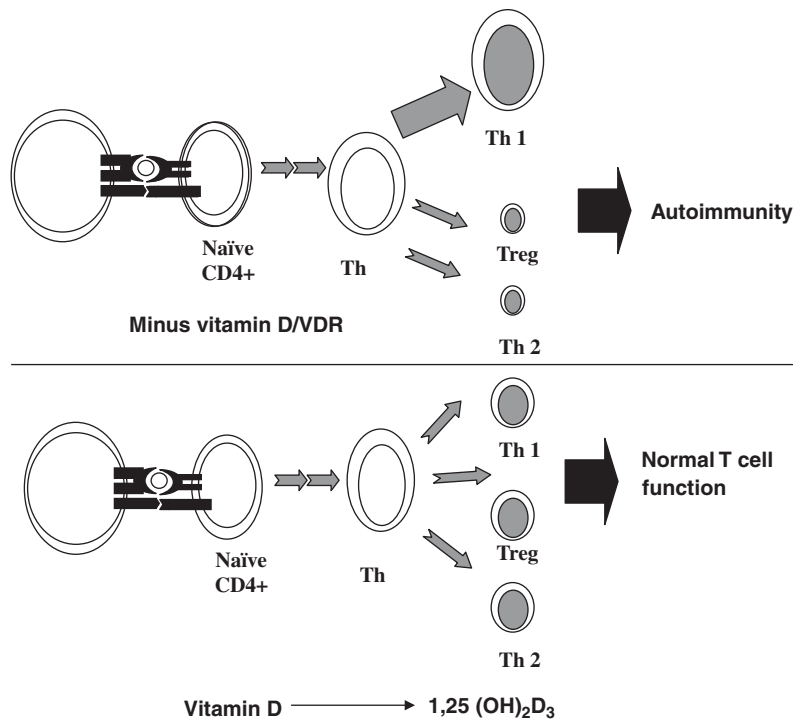


Fig. 1. A model for the role of vitamin D in CD4+ T cell development and function.

maintain adequate vitamin D levels or perhaps have polymorphisms in genes important for vitamin D metabolism, catabolism or function have an increased likelihood of developing MS/IBD. Vitamin D interventions should result in the increased availability of $1,25(\text{OH})_2\text{D}_3$ and a normalization of the T cell response which comes as a result of decreased Th1 cell function and increased regulatory and Th2 cell compartments. More needs to be done to determine the mechanisms by which vitamin D regulates autoimmune disease, what the optimal amount of vitamin D is for immune-regulation and whether there are genetic reasons why either production of $1,25(\text{OH})_2\text{D}_3$ from vitamin D or signaling through the VDR is altered in patients with autoimmune diseases.

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