Vitamin D and the Immune System: New Perspectives on an Old Theme

Martin Hewison, PhD

KEYWORDS
• Vitamin D • CYP27b1 • Toll-like receptor • Macrophage
• Cathelicidin • Regulatory T cells

HISTORICAL PERSPECTIVE

Nonclassic actions of vitamin D were first recognized 30 years ago when receptors for active 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) were detected in various neoplastic cell lines.¹,² Other studies immediately following this showed that binding of 1,25(OH)₂D₃ to the vitamin D receptor (VDR) promoted antiproliferative and prodifferentiation responses in cancer cells,³,⁴ highlighting an entirely new facet of vitamin D action. The spectrum of nonclassic responses to vitamin D was then extended to include actions on cells from the immune system.⁵,⁶ This interaction was further endorsed by the observation that some patients with the granulomatous disease sarcoidosis present with increased circulating levels of 1,25(OH)₂D₃ and associated hypercalcemia.⁷,⁸ In these patients the high serum level of 1,25(OH)₂D₃ is caused by increased activity of the enzyme 25-hydroxyvitamin D-1α-hydroxylase (1α-hydroxylase). However, in contrast to normal subjects in whom 1α-hydroxylase is classically localized in the kidney, the increased synthesis of 1,25(OH)₂D₃ in patients with sarcoidosis involves 1α-hydroxylase activity in disease-associated macrophages.⁹–¹¹ Thus, it was concluded that the immune system had the potential to synthesize 1,25(OH)₂D₃ and elicit autocrine or paracrine responses from immune cells expressing the VDR.¹²

Despite these early advances, the precise nature of the interaction between vitamin D and the immune system remained unresolved for many years. Some pieces of the puzzle were easier to complete than others. For example, it became evident that dysregulation of 1,25(OH)₂D₃ was not restricted to sarcoidosis but was a common feature of many granulomatous disorders and some forms of cancer.¹³ Likewise, at least in
vitro, it was possible to potently regulate a range of immune cell functions using 1,25(OH)₂D₃ or its synthetic analogs. However, the key remaining question was whether or not vitamin D could act as a physiologic regulator of normal immune responses. Answers to this question began to appear about 5 years ago and new information on the fundamental nature of vitamin D sufficiency/insufficiency has provided a fresh perspective on nonclassic actions of vitamin D. As a consequence, there is now a much broader acceptance that vitamin D plays an active role in regulating specific facets of human immunity. Details of this are reviewed and the possible effect of vitamin D insufficiency and vitamin D supplementation on normal immune function and human disease are discussed in this article.

VITAMIN D AND INNATE IMMUNITY

Macrophages, Vitamin D, and Cathelicidin

Consistent with the earlier seminal observations of extrarenal 1α-hydroxylase activity in patients with sarcoidosis, the effects of vitamin D on macrophage function have been central to many of the new observations implicating vitamin D in the regulation of immune responses. In common with natural killer cells (NK) and cytotoxic T lymphocytes (cytotoxic T cells), macrophages, and their monocyte precursors play a central role in initial nonspecific immune responses to pathogenic organisms or tissue damage, so-called cell-mediated immunity. Their role is to phagocytose pathogens or cell debris and then eliminate or assimilate the resulting waste material. In addition, macrophages can interface with the adaptive immune system by using phagocytic material for antigen presentation to T lymphocytes (T cells).

For many years, the key action of vitamin D on macrophages was believed to be its ability to stimulate differentiation of precursor monocytes to more mature phagocytic macrophages. This concept was supported by observations showing differential expression of VDR and 1α-hydroxylase during the differentiation of human monocytes/macrophages. The latter report also emphasized early studies showing that normal human macrophages were able to synthesize 1,25(OH)₂D₃ when stimulated with interferon gamma (IFNγ). Localized activation of vitamin D, coupled with expression of endogenous VDR was strongly suggestive of an autocrine or intracrine system for vitamin D action in normal monocytes/macrophages.

However, confirmation of such a mechanism was only obtained in 2006 when Liu and colleagues carried out DNA array analyses to define innate immunity genes that were specifically modulated in monocytes by *Mycobacterium tuberculosis*. In a seminal investigation both the VDR and the gene for 1α-hydroxylase (CYP27B1) were shown to be induced following activation of the principal pathogen recognition receptor for *M tuberculosis*, toll-like receptor 2/1 (TLR2/1). Subsequent experiments confirmed that precursor 25-hydroxyvitamin D₃ (25OHD₃) was able to induce intracrine VDR responses in monocytes that had been treated with a TLR2/1 activator. In particular, the TLR2/1-25OHD₃ combination stimulated expression of the antibacterial protein cathelicidin, so that vitamin D was able to promote monocyte killing of *M tuberculosis*. Notably, the ability to promote expression of the antibacterial protein following a TLR2/1 challenge was directly influenced by the 25OHD₃ status of the donor serum used for monocyte culture. More recently, the authors have shown that vitamin D supplementation in vivo can also enhance TLR2/1-induced cathelicidin expression. Cathelicidin was identified several years ago as a target for transcriptional regulation by 1,25(OH)₂D₃-ligated VDR, in that its gene promoter contains a functional vitamin D response element (VDRE). This VDRE occurs within a small interchangeable nuclear element (SINE) sequence which only seems to be present in
the cathelicidin gene promoter of higher primates, suggesting that vitamin D regulation of this facet of innate immunity is a relatively recent evolutionary development. Recent reports have underlined the importance of cathelicidin as a target for vitamin D but also suggest that this mechanism may be more complex than initially believed. As yet, the precise signal system by which TLR activation induces expression of VDR and 1\(\alpha\)-hydroxylase remains unclear. Promoter-reporter analysis of the events involved in transcriptional regulation of CYP27B1 suggest that TLR4-mediated induction of the enzyme involves JAK-STAT, MAP kinase and nuclear factor kappaB (NF-\(\kappa\)B) pathways, and that these synergize with IFN\(\gamma\)-mediated induction of CYP27B1. However, other studies have proposed that TLR2/1 induction of 1\(\alpha\)-hydroxylase occurs indirectly as a consequence of TLR2/1-induced interleukin (IL)-15, which is a potent inducer of CYP27B1 and 1\(\alpha\)-hydroxylase activity. In a similar fashion, IL-17A has been shown to enhance 1,25(OH)\(_2\)D\(_3\)-mediated induction of cathelicidin, although this response does not seem to involve transcriptional regulation of 1\(\alpha\)-hydroxylase or increased VDR sensitivity. One pathway that has been poorly studied in this regard concerns the enzyme 24-hydroxylase, which is conventionally considered to function by inactivating 1,25(OH)\(_2\)D\(_3\). The gene for 24-hydroxylase (CYP24) is potently induced by 25OHD\(_3\) following TLR2/1 activation of monocytes but, as yet, it is unclear whether this involves the nonmetabolic splice variant form of CYP24 known to be expressed by macrophages.

Regulation of the antibacterial protein by 1,25(OH)\(_2\)D\(_3\) has been described for a wide variety of cell types other than macrophages, including keratinocytes, lung epithelial cells, myeloid cell lines, and placental trophoblasts. In some cases, this seems to involve an intracrine response similar to that reported for monocytes. However, the mechanisms controlling local synthesis of 1,25(OH)\(_2\)D\(_3\) in these cells vary considerably. In keratinocytes, low baseline expression of 1\(\alpha\)-hydroxylase is enhanced following epidermal wounding by transforming growth factor beta (TGF\(\beta\)). The resulting increase in 1,25(OH)\(_2\)D\(_3\) concentration up-regulates expression of TLR2 and TLR4 by keratinocytes, thereby priming these cells for further innate immune responses to pathogens or tissue damage. By contrast, in trophoblasts, induction of cathelicidin and subsequent bacterial killing by 25OHD\(_3\) seems to be caused by constitutive 1\(\alpha\)-hydroxylase activity, which is not further enhanced by TLR activation. The latter may be a result of the rapid nonimmune induction of 1\(\alpha\)-hydroxylase and VDR that occurs within the placenta during early gestation.

Although most of the studies on vitamin D-mediated innate immunity have focused on the role of 1,25(OH)\(_2\)D\(_3\)-bound VDR as a pivotal transcriptional regulator of cathelicidin, it is also important to recognize that other ligands may interact with the VDR. For example, recent studies of biliary epithelial cells have shown that cathelicidin expression can be induced in a VDR-dependent fashion by bile salts. This provides a mechanism for maintaining biliary sterility, although additive effects of 1,25(OH)\(_2\)D\(_3\) also highlight a novel therapeutic application for vitamin D in the treatment of primary biliary cirrhosis. Conversely, other compounds may act to disrupt normal 1,25(OH)\(_2\)D\(_3\)-VDR-mediated immunity. The polycyclic aromatic hydrocarbon benzo[a]pyrene, a prominent product of cigarette smoking, has been shown to attenuate vitamin D-mediated induction of macrophage cathelicidin in a VDR-dependent fashion by stimulating expression of 24-hydroxylase and vitamin D catabolism. The precise mechanism by which this occurs has yet to be determined but these data suggest that some toxic compounds are actively detrimental to vitamin D-mediated immunity.

The observations described earlier show clearly that vitamin D is a potent stimulator of mechanisms associated with pathogen elimination. In subsequent sections the clinical importance of this with respect to vitamin D insufficiency and immune-related
diseases is discussed in more detail. However, 1 key question that immediately arises from the current observations is why there is a need to involve the vitamin D system in the TLR-induction of innate immunity. As previously described, VDR-mediated transcriptional regulation of cathelicidin is a relatively recent evolutionary change and was presumably advantageous when primates (including early Homo sapiens) were exposed to abundant sunlight, thereby priming high serum levels of vitamin D. Other benefits of incorporating vitamin D into innate immune regulation include the fact that it is associated with key feedback control pathways. As already mentioned, vitamin D has its own catabolic enzyme in the form of 24-hydroxylase, which sensitively attenuates responses to 1,25(OH)2D3 and, in the case of the CYP24 splice variant, may also attenuate synthesis of this vitamin D metabolite. However, vitamin D may also provide feedback regulation of immune activation pathways in that 1,25(OH)2D3 has been shown to potently down-regulate expression of monocyte TLR2 and TLR4, thereby suppressing inflammatory responses that are normally activated by these receptors. Thus, by using CYP24 and TLR regulatory mechanisms, vitamin D may help to promote appropriate innate immune responses while preventing an over elaboration of innate immune responses and the tissue damage frequently associated with this.

Dendritic Cells and Antigen Presentation

In addition to the phagocytic acquisition and elimination of pathogens and cell debris, innate immunity also involves the presentation of resultant antigen to cells involved in the adaptive arm of the immune system (Fig. 1). Although several cells are able to do this, the most well-recognized group of professional antigen-presenting cells (APCs) are dendritic cells (DCs). Expression of VDR by purified tissue DCs was first reported in 1987. Subsequent studies using populations of DCs isolated from skin (Langerhans cells) provided evidence that 1,25(OH)2D3 could act to attenuate antigen presentation. However, it was not until the later advent of in vitro monocyte-derived DC models that the effects of vitamin D metabolites on antigen presentation were fully elucidated. In 2000, parallel studies by the Adorini and Kumar groups showed that 1,25(OH)2D3 and its synthetic analogs inhibited the maturation of monocyte-derived DCs, thereby suppressing their capacity to present antigen to T cells. Based on these observations, it was proposed that vitamin D could act to promote tolerance and this was endorsed by studies of pancreatic islet transplantation in which lower rejection rates were observed in 1,25(OH)2D3-treated mice. Crucially this response to 1,25(OH)2D3 appeared to be caused by decreased DC maturation and concomitant enhancement of suppressor or regulatory T cells (Treg). Further studies have underlined the importance of Treg generation as part of the interaction between vitamin D and the immune system, and this is discussed in greater detail in later sections of this article.

Although regulation of DC maturation represents a potential target for 1,25(OH)2D3 and its synthetic analogs as treatment of autoimmune disease and host-graft rejection, another perspective was provided by the observation that DCs express 1α-hydroxylase in a similar fashion to macrophages. Data from monocyte-derived DCs showed that 1α-hydroxylase expression and activity increases as DCs differentiate towards a mature phenotype. Functional analyses showed that treatment with 25OHD3 suppresses DC maturation and inhibits T-cell proliferation, confirming the existence of an intracrine pathway for vitamin D similar to that observed for macrophages. Mature DCs showed lower levels of VDR than immature DCs or monocytes. This reciprocal organization of 1α-hydroxylase and VDR expression may be advantageous in that mature antigen-presenting DCs may be relatively insensitive to 1,25(OH)2D3, thereby allowing induction of an initial T-cell response. However, the
high levels of 1,25(OH)2D3 being synthesized by these cells can to act on VDR-expressing immature DCs and thus prevent their further development. In this way, paracrine action of locally produced 1,25(OH)2D3 allows initial presentation of antigen to T cells while preventing continued maturation of DCs and over stimulation of T cells.

Although DCs are heterogeneous in terms of their location, phenotype, and function, they are broadly divided into 2 groups based on their origin. Myeloid (mDCs) and plasmacytoid (pDCs) express different types of cytokines and chemokines and seem to exert complementary effects on T-cell responses, with mDCs being the most effective APCs and pDCs being more closely associated with immune tolerance. Therefore 1,25(OH)2D3 preferentially regulates mDCs, suggesting that the key effect of vitamin D in this instance is to suppress activation of naive T cells. Although in this study pDCs showed no apparent immune response to 1,25(OH)2D3, this does not preclude a role for vitamin D in the regulation of tolerogenic responses. One possibility is that local intracrine synthesis of 1,25(OH)2D3 is more effective in achieving these responses. Alternatively, 1,25(OH)2D3 synthesized by pDCs may regulate tolerance through paracrine effects on VDR-expressing T cells. This is discussed in further detail in the following section.

VITAMIN D AND ADAPTIVE IMMUNITY

Vitamin D and T-cell Function

Resting T cells express almost undetectable levels of VDR, but levels of the receptor increase as T cells proliferate following antigenic activation.
a consequence, initial studies of the effects of vitamin D on T cells focused on the ability of 1,25(OH)\(_2\)D\(_3\) to suppress T-cell proliferation.\(^{48-50}\) However, the recognition that CD4\(^+\) effector T cells were capable of considerable phenotypic plasticity, suggested that vitamin D might also influence the phenotype of T cells. Lemire and colleagues\(^{51}\) first reported that 1,25(OH)\(_2\)D\(_3\) preferentially inhibited T helper 1 (Th1) cells, which are a subset of CD4\(^+\) effector T cells closely associated with cellular, rather than humoral, immune responses. Subsequent studies confirmed this observation and demonstrated that the cytokine profile of 1,25(OH)\(_2\)D\(_3\)-treated human T cells was consistent with Th2 cells, a subset of CD4\(^+\) T cells associated with humoral (antibody)-mediated immunity.\(^{52,53}\) The conclusion from these observations was that vitamin D promotes a T-cell shift from Th1 to Th2 and thus might help to limit the potential tissue damage associated with Th1 cellular immune responses. However, the validity of this generalization was called into question by studies using mouse T cells in which 1,25(OH)\(_2\)D\(_3\) was shown to inhibit cytokines associated with Th1 (IFN\(\gamma\)) and Th2 (IL-4). Subsequent analysis of immune cells from the VDR gene knockout mouse added further confusion by showing that these animals had reduced (rather than the predicted increased) levels of Th1 cells.\(^{54}\) Thus, although in vitro vitamin D seems to broadly support a shift from Th1 to Th2 in CD4\(^+\) cells, it seems likely that in vivo its effects on T cells are more complex.

The T-cell repertoire has continued to expand with the characterization of another effector T-cell lineage distinct from Th1 or Th2 cells, termed Th17 cells because of their capacity to synthesize IL-17.\(^{55,56}\) Th17 cells play an essential role in combating certain pathogens but they have also been linked to tissue damage and inflammation.\(^{57,58}\) The precise role of vitamin D as a regulator of Th17 cells has yet to be fully elucidated but studies of animal models of the gastrointestinal inflammatory disease colitis have shown that treatment with 1,25(OH)\(_2\)D\(_3\) reduces expression of IL-17,\(^{59}\) and loss of 1,25(OH)\(_2\)D\(_3\) as a result of CYP27b1 gene ablation leads to increased levels of this cytokine.\(^{60}\) Thus, it possible that vitamin D exerts some of its effects on inflammation and autoimmune disease through the regulation of Th17 cells.

A fourth group of CD4\(^+\) T cells exert suppressor rather than effector functions and are known as regulatory T cells or Tregs. In view of its early recognition as a suppressor of T-cell proliferation, it was anticipated that vitamin D would have effects on Tregs, and indeed in 2002 Barrat and colleagues\(^{61}\) showed that 1,25(OH)\(_2\)D\(_3\), in conjunction with glucocorticoids, potently stimulated the generation of IL-10–producing CD4\(^+\)/CD25\(^+\) Tregs. Subsequent reports indicated that 1,25(OH)\(_2\)D\(_3\) alone can induce Tregs,\(^{62}\) and it seems that preferential differentiation of Tregs is a pivotal mechanism linking vitamin D and adaptive immunity, with potential beneficial effects for autoimmune disease and host-graft rejection.\(^{63-65}\) This immunosuppressive mechanism is likely to be mediated by the induction of tolerogenic DCs as described in the previous section of the review,\(^{41,66,67}\) but direct effects on T cells may also be important.\(^{68}\) In this latter study, it was notable that 1,25(OH)\(_2\)D\(_3\) increased IL-10 secretion and TLR9 expression by Tregs, suggesting a novel link between innate and adaptive immune responses.\(^{58}\)

Relative to the amount of literature on CD4\(^+\) effector cells, our understanding of the effects of vitamin D on CD8\(^+\) suppressor T cells remains somewhat limited. In contrast to CD4\(^+\) cells, CD8\(^+\) cells show poor antiproliferative response to 1,25(OH)\(_2\)D\(_3\).\(^{50,69,70}\) However, VDR expression seems to be abundant in CD8\(^+\) cells suggesting that they are still potential targets for 1,25(OH)\(_2\)D\(_3\). Indeed subsequent reports have shown that 1,25(OH)\(_2\)D\(_3\) actively regulates cytokine production by CD8\(^+\) cells,\(^{71}\) and can also regulate the proliferation of CD8\(^+\) cells following specific immune stimuli.\(^{72}\) Despite
this, 1,25(OH)\(_2\)D\(_3\) does not seem to have a significant effect on animal disease models such as experimental autoimmune encephalomyelitis in which CD8\(^+\) cells have been implicated.\(^{73}\)

Although many of the studies linking 1,25(OH)\(_2\)D\(_3\) with adaptive immunity have focused on changes in T-cell proliferation and phenotype, it is important to recognize that other facets of T-cell function may also be affected by the hormone. In particular, recent studies have shown that vitamin D can exert powerful effects on the homing of T cells to specific tissues. Initial studies suggested that 1,25(OH)\(_2\)D\(_3\) acts to inhibit migration of T cells to lymph nodes.\(^{74}\) However, more recent reports have shown an active role for vitamin D in promoting homing of T cells to the skin via up-regulation of chemokine receptor 10 (CCR10), the ligand for which, CCL27, is expressed by epidermal keratinocytes.\(^{75}\) This T-cell homing response was induced by 25OHD\(_3\) as well as 1,25(OH)\(_2\)D\(_3\) and the author suggested that DCs and T cells were possible sources of the local 1\(\alpha\)-hydroxylase activity.\(^{75}\) In contrast to its positive effect on epidermal T-cell homing, vitamin D seems to exert a negative effect on chemokines and chemokine receptors associated with the gastrointestinal tract.\(^{75}\) However, it seems likely that this is highly T-cell selective as newer studies using the VDR gene knockout mouse have shown aberrant gastrointestinal migration of a subset of CD8\(^+\) cells, and this effect seems to be closely linked to the increased risk of colitis in VDR knockout mice.\(^{76}\)

**Vitamin D and B-cell Function**

Like T cells, active but not inactive B cells express the VDR.\(^{77}\) Consequently, initial studies indicated that 1,25(OH)\(_2\)D\(_3\) could directly regulate B-cell proliferation\(^{78}\) and immunoglobulin (Ig) production.\(^{77}\) Subsequent work contradicted this, suggesting instead that the ability of 1,25(OH)\(_2\)D\(_3\) to suppress proliferation and Ig production was caused by indirect effects mediated via helper T cells.\(^{79}\) However, more recent reports have shown that 1,25(OH)\(_2\)D\(_3\) does indeed exert direct effects on B-cell homeostasis.\(^{80}\) In addition to confirming direct VDR-mediated effects on B-cell proliferation and Ig production, this study also highlighted the ability of 1,25(OH)\(_2\)D\(_3\) to inhibit the differentiation of plasma cells and class-switched memory cells, suggesting a potential role for vitamin D in B-cell–related disorders such as systemic lupus erythematosus. Expression of CYP27b1 was also detected in B cells, indicating that B cells may be capable of autocrine/intracrine responses to vitamin D.\(^{80}\) Indeed, this may be common to lymphocytes in general as CYP27b1 expression has also been detected in T cells.\(^{75}\)

**VITAMIN D, THE IMMUNE SYSTEM AND HUMAN HEALTH**

For many years vitamin D status was defined simply by whether or not the patient had symptoms of the bone disease rickets (osteomalacia in adults). However, an entirely new perspective on vitamin D status has arisen from the observation that serum levels of the main circulating form of vitamin D (25OHD\(_3\)) as high as 75 nM correlate inversely with parathyroid hormone.\(^{81}\) This, has prompted the introduction of a new term, vitamin D insufficiency, defined by serum levels of 25OHD\(_3\) that are suboptimal (<75 nM) but not necessarily rachitic (<20 nM).\(^{82}\) Unlike serum concentrations of 1,25(OH)\(_2\)D\(_3\), which are primarily defined by the endocrine regulators of the vitamin D–activating enzyme, 1\(\alpha\)-hydroxylase, circulating levels of 25OHD\(_3\) are a direct reflection of vitamin D status, which for any given individual depends on access to vitamin D either through exposure to sunlight or through dietary intake. The net effect of this is that vitamin D status can vary significantly in populations depending on geographic,
social, or economic factors. As a result of these new parameters for vitamin D status, a consensus statement from the 13th Workshop on Vitamin D concluded that vitamin D insufficiency was a worldwide epidemic. Moreover, recent studies have shown that in the last 10 years alone, serum vitamin D levels have on average fallen by 20%. The key question now being considered is what is the physiologic and clinical effect of global vitamin D insufficiency beyond classic bone diseases such as rickets? Epidemiologic studies have highlighted possible links between vitamin D insufficiency and a wide range of human diseases. The final section of the article describes 4 of the key clinical problems that have been linked to the immunomodulatory properties of vitamin D.

Vitamin D and Tuberculosis

The observation that vitamin D acts to promote innate immune responses to TLR activation by *M. tuberculosis* has provided a new perspective on observations made many decades ago on the beneficial effects of ultraviolet light exposure on tuberculosis (TB). As a consequence this has become the most well-studied facet of the interaction between vitamin D and innate immunity. Initial studies to assess the effects of 25OHD status on ex vivo macrophage function have shown that supplementation with a single oral dose of 2.5 mg of vitamin D enhances the ability of recipient macrophages to combat Bacille Calmette Guérin infection in vitro. The potential benefits of vitamin D as treatment of TB have been further endorsed by a study that showed that adjunct vitamin D supplementation (0.25 mg vitamin D/d) of TB patients receiving conventional therapy for the disease reduced the time for sputum smear conversion from acid-fast bacteria (AFB)-positive to AFB-negative status. A recent, double-blind, randomized, placebo-controlled trial showed that vitamin D supplementation had no effect on clinical outcomes or mortality amongst TB patients, although it should be emphasized that none of the supplemented patients in this study showed a significant increase in serum vitamin D levels.

Vitamin D and Multiple Sclerosis

Several epidemiology studies have reported an association between vitamin D insufficiency and the incidence and/or severity of the autoimmune disease multiple sclerosis (MS) (reviewed in Ref. 88). These observations have been supported by analysis of animal models, such as the experimental autoimmune encephalomyelitis (EAE) mouse, which show increased disease severity under dietary vitamin D restriction. Conversely, administration of 1,25(OH)2D3 to EAE mice confers disease protection through effects on cytokine synthesis and apoptosis of inflammatory cells. Some effects of 1,25(OH)2D3 on EAE seem to be dependent on IL-10 activity.

Vitamin D and Type 1 Diabetes

In common with MS, published reports suggest that there is a link between vitamin D deficiency and another autoimmune disease, type 1 diabetes (reviewed in Ref. 92). Low circulating levels of 25OH3 have been reported in adolescents at the time of diagnosis of type 1 diabetes, and other data have documented the beneficial effects of vitamin D supplementation in protecting against type 1 diabetes. Another strand of evidence linking vitamin D with type 1 diabetes stems from extensive genetic analyses on the physiologic effect of inherited variations in the genes for various components of the vitamin D metabolic and signaling system. Previous studies have indicated that some VDR gene haplotypes confer protection against diabetes, and more recently this has been expanded to show that genetic variants of the CYP27b1 gene also affect susceptibility to type 1 diabetes. Similar to animal model
studies for MS, in vivo use of the nonobese diabetic (NOD) mouse as a model for type 1 diabetes has shown increased disease severity under conditions of dietary vitamin D restriction.97

Vitamin D and Crohn Disease

Several strands of evidence have linked vitamin D to the dysregulated immune responses observed with inflammatory bowel diseases such as Crohn disease. First, epidemiology suggests that patients with Crohn disease have decreased serum levels of 25OHD3.98–100 Second, studies in vivo using various animal models indicate that 1,25(OH)2D3 plays a crucial role in the pathophysiology of experimentally induced forms of inflammatory bowel disease.60,101–103 Third, expression of 1α-hydroxylase has been detected in the human colon,104 with the vitamin D–activating enzyme being up-regulated in disease-affected tissue from patients with Crohn disease.105 In the case of the latter, dysregulated colonic expression of 1α-hydroxylase was associated with increased circulating levels of 1,25(OH)2D3 indicating that, as with sarcoidosis, localized synthesis of this vitamin D metabolite can spill over into the general circulation under conditions of persistent disease.105 Current studies have implicated aberrant innate immune handling of enteric microbiota as an initiator of the adaptive immune damage associated with Crohn disease.106 It is thus tempting to speculate that effects of vitamin D on this disease may involve the activation of innate immunity, together with the suppression of adaptive immunity and associated inflammation.

SUMMARY

It is almost 30 years since an interaction between vitamin D and the immune system was first documented. Although this was initially proposed as a nonclassic effect of vitamin D associated with granulomatous diseases, our current view is now changed considerably. Recent studies have shown a potential physiologic role for vitamin D in regulating normal innate and adaptive immunity. Future studies now need to focus on the clinical implications of vitamin D–mediated immunity and, in particular, the possible beneficial effects of supplementary vitamin D with respect to infectious and autoimmune diseases.

REFERENCES


42. O’Garra A, Barrat FJ. In vitro generation of IL-10-producing regulatory CD4+ T cells is induced by immunosuppressive drugs and inhibited by Th1- and Th2-inducing cytokines. Immunol Lett 2003;85:135.


73. Meehan TF, DeLuca HF. CD8(+) T cells are not necessary for 1alpha,25-dihydroxyvitamin D(3) to suppress experimental autoimmune encephalomyelitis in mice. Proc Natl Acad Sci U S A 2002;99:5557.
101. 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.
