Vitamin D and the immune system: new perspectives on an old theme

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Synopsis

Interaction with the immune system is one of the most well-established non-classical effects of vitamin D. For many years this was considered to be a manifestation of granulomatous diseases such as sarcoidosis, where synthesis of active 1,25-dihydroxyvitamin D_3 (1,25(OH)$_2$D$_3$) is known to be dysregulated. However, recent reports have supported a role for 1,25(OH)$_2$D$_3$ in mediating normal function of both the innate and adaptive immune systems. Crucially, these effects appear to be mediated via localized autocrine or paracrine synthesis of 1,25(OH)$_2$D$_3$ from precursor 25-hydroxyvitamin D_3 (25OHD$_3$), the main circulating metabolite of vitamin D. As such, the ability of vitamin D to influence normal human immunity will be highly dependent on the vitamin D status of individuals, and may lead to aberrant response to infection or autoimmunity in those who are vitamin D-insufficient. The potential health significance of this has been underlined by increasing awareness of impaired vitamin D status in populations across the globe. The following review article will describe in more detail some of the recent developments with respect to vitamin D and the immune system, together with possible clinical implications.

Keywords

vitamin D; CYP27b1; toll-like receptor; macrophage; cathelicidin; regulatory T-cells

Introduction

Historical perspective

Non-classical actions of vitamin D were first recognized thirty years ago when receptors for active 1,25-dihydroxyvitamin D_3 (1,25(OH)$_2$D$_3$) were detected in various neoplastic cells lines [23,59]. Other studies immediately following this showed that binding of 1,25(OH)$_2$D$_3$ to the vitamin D receptor (VDR) promoted antiproliferative and prodifferentiation responses in cancer cells [1,18], highlighting an entirely new facet of vitamin D action. The spectrum of non-classical responses to vitamin D was then extended to include actions on cells from the immune system [2,13]. This interaction was further endorsed by the observation that some patients with the granulomatous disease sarcoidosis present with elevated circulating levels of 1,25

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$(OH)_2D_3$ and associated hypercalcemia [11,72]. In these patients the high serum $1,25(OH)_2D_3$ is due to increased activity of the enzyme 25-hydroxyvitamin D-1α-hydrooxylase (1α-hydroxylase). However, in contrast to normal subjects where 1α-hydroxylase is classically localized in the kidney, the increased synthesis of $1,25(OH)_2D_3$ in patients with sarcoidosis involves 1α-hydroxylase activity in disease-associated macrophages [4,6,9]. Thus, it was concluded that the immune system had the potential to both synthesize $1,25(OH)_2D_3$ and elicit autocrine or paracrine responses from immune cells expressing the vitamin D receptor [38].

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 $1,25(OH)_2D_3$ was not restricted to sarcoidosis but was a common feature of many granulomatous disorders and some forms of cancer [39]. Likewise, at least in vitro, it was possible to potently regulate a range of immune cell functions using $1,25(OH)_2D_3$ or its synthetic analogs [35,97]. However, the key remaining question concerned whether or not vitamin D could act as a physiological regulator of normal immune responses. Answers to this question began to appear about five years ago and new information on the fundamental nature of vitamin D sufficiency/insufficiency has provided a fresh perspective on non-classical 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. This will be detailed in the following review together with discussion on the possible impact of vitamin D insufficiency and vitamin D supplementation on normal immune function and human disease.

Vitamin D and innate immunity

Macrophages, vitamin D and cathelicidin

Consistent with the earlier seminal observations of extra-renal 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 non-specific 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 utilizing phagocytic material for antigen presentation to T-lymphocytes (T-cells).

For many years, the key action of vitamin D on macrophages was thought to be its ability to stimulate differentiation of precursor monocytes to more mature phagocytic macrophages [1,2,45,93]. This concept was supported by observations showing differential expression of VDR and 1α-hydroxylase during the differentiation of human monocytes macrophages [49]. The latter report also emphasized early studies showing that normal human macrophages were able to synthesize $1,25(OH)_2D_3$ when stimulated with interferon gamma (IFNγ) [46]. 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 Robert Modlin and colleagues carried out DNA array analyses to define innate immunity genes that were specifically modulated in monocytes by *Mycobacterium tuberculosis* (*M. tb*). 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. tb*, toll-like receptor 2/1 (TLR2/1) [56]. Subsequent experiments confirmed that precursor $25OHD_3$ was able to induce intracrine VDR responses in monocytes that had been treated with a TLR2/1 activator. In particular, the TLR2/1–$25OHD_3$ combination stimulated expression of the antibacterial

protein cathelicidin, so that vitamin D was able to promote monocyte killing of *M. tb* [56]. Notably, the ability to promote expression of the antibacterial protein following a TLR2/1 challenge was directly influenced by the $25OHD_3$ status of the donor serum used for monocyte culture [56]. More recently, we have shown that vitamin D supplementation in vivo can also enhance TLR2/1-induced cathelicidin expression [5]. Cathelicidin was identified several years ago as a target for transcriptional regulation by $1,25(OH)_2D_3$-liganded VDR, in that its gene promoter contains a functional vitamin D response element (VDRE) [30,100]. Interestingly, this VDRE occurs within a small interchangeable nuclear element (SINE) sequence which only appears 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 [30].

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 thought. As yet, the precise signal system by which TLR activation induces expression of VDR and 1α-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 kappB (NF-κB) pathways, and that these synergize with IFNγ-mediated induction of CYP27B1 [92]. However, other studies have proposed that TLR2/1 induction of 1α-hydroxylase occurs indirectly as a consequence of TLR2/1 induced interleukin-15 (IL-15) which is a potent inducer of CYP27B1 and 1α-hydroxylase activity [50]. In a similar fashion, interleukin 17A (IL-17A) has been shown to enhance $1,25(OH)_2D_3$-mediated induction of cathelicidin, although this response does not appear to involve transcriptional regulation of 1α-hydroxylase or increased VDR sensitivity [77]. One pathway that has been poorly studied in this regard concerns the enzyme 24-hydroxylase, which is conventionally considered to function by inactivating $1,25(OH)_2D_3$. The gene for 24-hydroxylase (CYP24) is potently induced by $25OHD_3$ following TLR2/1 activation of monocytes [56] but, as yet, it is unclear whether this involves the non-metabolic splice variant form of CYP24 known to be expressed by macrophages [82].

Regulation of the antibacterial protein by $1,25(OH)_2D_3$ has been described for a wide variety of cell types other than macrophages, including keratinocytes [84,85,100], lung epithelial cells [104], myeloid cell lines [30,85,100] and placental trophoblasts [54]. In some cases [54,84], this appears to involve an intracrine response similar to that reported for monocytes. However, the mechanisms controlling local synthesis of $1,25(OH)_2D_3$ in these cells vary considerably. In keratinocytes, low baseline expression of 1α-hydroxylase is enhanced following epidermal wounding by transforming growth factor beta (TGFβ) [84]. The resulting rise in $1,25(OH)_2D_3$ concentrations upregulates expression of TLR2 and TLR4 by keratinocytes, thereby priming these cells for further innate immune responses to pathogens or tissue damage [84]. By contrast, in trophoblasts, induction of cathelicidin and subsequent bacterial killing by $25OHD_3$ appears to be due to constitutive 1α-hydroxylase activity, which is not further enhanced by TLR activation [54]. The latter may be due to the rapid non-immune induction of 1α-hydroxylase and VDR which occurs within the placenta during early gestation [24].

Although most of the studies of vitamin D-mediated innate immunity have focused on the role of $1,25(OH)_2D_3$-bound VDR as a pivotal transcriptional regulator of cathelicidin, it is also important to recognize that other ligands may interact with the VDR [58]. For example, recent studies of bilary epithelial cells have shown that cathelicidin expression can be induced in a VDR-dependent fashion by bile salts [19]. This provides a mechanism for maintaining bilary sterility, although additive effects of $1,25(OH)_2D_3$ also highlight a novel therapeutic application for vitamin D in the treatment of primary bilary cirrhosis. Conversely, other compounds may act to disrupt normal $1,25(OH)_2D_3$-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 cathelcidin in a VDR-dependent fashion by stimulating expression of 24-hydroxylase, and vitamin D catabolism [64]. 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 detailed above 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, one 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 $1,25(OH)_2D_3$ and, in the case of the CYP24 splice variant, may also attenuate synthesis of this vitamin D metabolite [82]. However, vitamin D may also provide feedback regulation of immune activation pathways in that $1,25(OH)_2D_3$ has been shown to potently downregulate expression of monocyte TLR2 and TLR4, thereby suppressing inflammatory responses that are normally activated by these receptors [83]. Thus, by utilizing both CYP24 and TLR regulatory mechanisms, vitamin D may help to promote appropriate innate immune responses whilst 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 (see Figure 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[15]. Subsequent studies using populations of DCs isolated from skin (Langerhans cells) provided evidence that $1,25(OH)_2D_3$ could act to attenuate antigen presentation [20]. 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 $1,25(OH)_2D_3$[76] and its synthetic analogs [34] 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 $1,25(OH)_2D_3$-treated mice [32]. Crucially this response to $1,25(OH)_2D_3$ appeared to be due to decreased DC maturation and concomitant enhancement of suppressor or regulatory T-cells (Treg) [32]. Further studies have underlined the importance of Treg generation [68] as part of the interaction between vitamin D and the immune system and this is discussed in greater detail in later sections of this review.

Although regulation of DC maturation represents at potential target for $1,25(OH)_2D_3$ and its synthetic analogs as treatment for autoimmune disease and host-graft rejection, another perspective was provided by the observation that DCs express 1α-hydroxylase in a similar fashion to macrophages [25,40]. Data from monocyte-derived DCs showed that 1α-hydroxylase expression and activity increases as DCs differentiate towards an a mature phenotype [40]. Functional analyses showed that treatment with 25OHD$_3$ suppresses DC maturation and inhibits T-cell proliferation, confirming the existence of an intracrine pathway for vitamin D

similar to that observed for macrophages [40]. Interestingly, mature DCs showed lower levels of VDR than immature DCs or monocytes [40]. 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)$_2$D$_3$, thereby allowing induction of an initial T-cell response. However, the high levels of 1,25(OH)$_2$D$_3$ being synthesized by these cells will be able to act on VDR-expressing immature DCs and thus prevent their further development [41]. In this way, paracrine action of locally produced 1,25(OH)$_2$D$_3$ will allow initial presentation of antigen to T-cells whilst 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 two groups based on their origin. Myeloid (mDCs) and plasmacytoid (pDCs) express different types of cytokines and chemokines and appear to exert complementary effects on T-cell responses, with mDCs being the most effective APCs [57] and pDCs being more closely associated with immune tolerance [91]. It is therefore interesting to note that 1,25(OH)$_2$D$_3$ preferentially regulates mDCs, suggesting that the key effect of vitamin D in this instance is to suppress activation of naïve T-cells. Although in this study pDCs showed no apparent immune response to 1,25(OH)$_2$D$_3$, 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)$_2$D$_3$ will be more effective in achieving these responses. Alternatively, 1,25(OH)$_2$D$_3$ 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 [44,66,78]. As 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 [44,66,78]. 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 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 [52]. 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 [14,70]. 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 both Th1 (IFNγ) and Th2 (interleukin-4, 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 elevated) levels of Th1 cells [69]. Thus, whilst in vitro vitamin D appears 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 interleukin-17 (IL-17) [36,101]. Th17 cells play an essential role in combating certain pathogens but they have also been linked to tissue damage and inflammation [12,48]. The precise role of vitamin D as a regulator of Th17 cells has yet to be fully elucidated but it is interesting to note that 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[21], whilst loss of 1,25(OH)$_2$D$_3$ as a result of CYP27b1 gene ablation leads to elevated levels of this cytokine [55].

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 O'Garra and colleagues demonstrated that 1,25(OH)$_2$D$_3$, in conjunction with glucocorticoids, potently stimulated the generation of interleukin-10 (IL-10)-producing CD4^{+}/CD25^{+} Tregs [10]. Subsequent reports indicated that 1,25(OH)$_2$D$_3$ alone can induce Tregs [31], and it appears 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 [33,62,89]. This immunosuppressive mechanism is likely to be mediated by the induction of tolerogenic DCs as described in the previous section of the review [7,22,32], but direct effects on T-cells may also be important [95]. In this latter study, it was notable that 1,25(OH)$_2$D$_3$ increased both IL-10-secretion and TLR9 expression by Tregs, suggesting a novel link between innate and adaptive immune responses [95].

Relative to the wealth 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^{+} show poor antiproliferative response to 1,25(OH)$_2$D$_3$[78,98,99]. However, VDR expression appears 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 [103], and can also regulate the proliferation of CD8^{+} cells following specific immune stimuli [43]. Despite this, 1,25(OH)$_2$D$_3$ does not appear to have a significant impact on animal disease models such as experimental autoimmune encephalomyelitis where CD8^{+} cells have been implicated [65].

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 [94]. However, more recent reports have demonstrated an active role for vitamin D in promoting homing of T-cells to the skin via upregulation of chemokine receptor 10 (CCR10), the ligand for which, CCL27, is expressed by epidermal keratinocytes [87]. Notably this T-cell homing response was induced by 25OHD$_3$ as well as 1,25(OH)$_2$D$_3$ and the author suggested that both DCs and T-cells were possible sources of the local 1α-hydroxylase activity [87]. In contrast to its positive effect on epidermal T-cell homing, vitamin D appears to exert a negative effect on chemokines and chemokine receptors associated with the GI tract [87]. However, it seems likely that this is will be highly T-cell selective as newer studies using the VDR gene knockout mouse have demonstrated aberrant GI migration of a subset of CD8^{+} cells, and this effects appears to be closely linked to the increased risk of colitis in VDR knockout mice [105].

Vitamin D and B-cell function

Like T-cells, active but not inactive B-cells express the VDR [79]. Consequently, initial studies indicated that 1,25(OH)$_2$D$_3$ could directly regulate B-cell proliferation [86] and immunoglobulin (Ig) production [79]. Subsequent work contradicted this, suggesting instead that the ability of 1,25(OH)$_2$D$_3$ to suppress proliferation and immunoglobulin (Ig) production was due to indirect effects mediated via helper T-cells [51]. However, more recent reports have demonstrated that 1,25(OH)$_2$D$_3$ does indeed exert direct effects on B cell homeostasis [17]. 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 erythamtosus. Notably, expression of CYP27b1 was also detected in B-cells, indicating that B-cells may be capable of autocrine/intracrine responses to vitamin D [17]. Indeed, this may be common to lymphocytes in general as CYP27b1 expression has also been detected in T-cells [87].

Vitamin D, the immune system and human health

For many years vitamin D status was defined simply by whether or not the patient in question exhibited 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 [16]. This, has prompted the introduction of a new term - vitamin D 'insufficiency' - defined by serum levels of $25OHD_3$ that are sub-optimal (< 75 nM) but not necessarily rachitic (< 20 nM) [42]. Unlike serum concentrations of $1,25(OH)_2D_3$, which are primarily defined by the endocrine regulators of the vitamin D-activating enzyme, 1α-hydroxylase, circulating levels of $25OHD_3$ are a direct reflection of vitamin D status, which for any given individual will depend 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 geographical, 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 ten years alone, serum vitamin D levels have on average fallen by 20% [28]. The key question now being considered is what is the physiological and clinical impact of global vitamin D insufficiency beyond classical bone diseases such as rickets? Epidemiological studies have highlighted possible links between vitamin D insufficiency and a wide range of human diseases [42]. The final section of the review will describe four of the key clinical problems which 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. tb* [56], has provided a new perspective on observations made many decades ago concerning the beneficial effects of UV light exposure on the disease TB. As a consequence this has become the most well studied facet of the interaction between vitamin D and innate immunity [60]. 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 vitamin D enhances the ability of recipient macrophages to combat BCG infection *in vitro* [61]. The potential benefits of vitamin D as treatment for tuberculosis (TB) have been further endorsed by a study which showed that adjunct vitamin D supplementation (0.25 mg vitamin D/day) 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 [67]. 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 rise in serum vitamin D levels [102].

Vitamin D and multiple sclerosis

Several epidemiology studies have reported association between vitamin D insufficiency and the incidence and/or severity of the autoimmune disease multiple sclerosis (MS) (reviewed in [80]. These observations have been supported by analysis of animal models such as the experimental autoimmune encephalomyelitis (EAE) mouse, which shows increased disease severity under dietary vitamin D restriction [88]. Conversely administration of $1,25(OH)_2D_3$ to EAE mice confers disease protection through effects on cytokine synthesis and apoptosis of

inflammatory cells [75,90]. Some effects of 1,25(OH)$_2$D$_3$ on EAE appear to be dependent on IL-10 activity [89].

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 [63]). Low circulating levels of 25OHD$_3$ have been reported in adolescents at the time of diagnosis of type 1 diabetes [53], and other data have documented the beneficial effects of vitamin D supplementation in protecting against type 1 diabetes [37]. Another strand of evidence linking vitamin D with type 1 diabetes stems from the extensive genetic analyses that have explored the physiological impact 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 [81] and more recently this has been expanded to show that genetic variants of the CYP27b1 gene also affect susceptibility to type 1 diabetes [8]. Finally, in a similar fashion to animal model studies for MS, in vivo use of the non-obese diabetic (NOD) mouse as a model for type 1 diabetes has shown increased disease severity under conditions of dietary vitamin D restriction [29].

Vitamin D and Crohn's disease

Several strands of evidence have linked vitamin D to the dysregulated immune responses observed with inflammatory bowel diseases such as Crohn's disease. Firstly, epidemiology suggests that patients with Crohn's disease have decreased serum levels of 25OHD$_3$[73,74,96]. Secondly, studies in vivo using various animal models indicate that 1,25(OH)$_2$D$_3$ plays a crucial role in the pathophysiology of experimentally-induced forms of inflammatory bowel disease [26,27,47,55]. Finally, expression of 1α-hydroxylase has been detected in the human colon [106], with the vitamin D-activating enzyme being upregulated in disease-affected tissue from patients with Crohn's disease [3]. In the case of the latter, dysregulated colonic expression of 1α-hydroxylase was associated with increased circulating levels of 1,25(OH)$_2$D$_3$ indicating that, as with sarcoidosis, localized synthesis of this vitamin D metabolite can spill-over into the general circulation under conditions of persistent disease [3]. Intriguingly, current studies have implicated aberrant innate immune handling of enteric microbiota as an initiator of the adaptive immune damage associated with Crohn's disease [71]. It is thus tempting to speculate that effects of vitamin D on this disease may involve both the activation of innate immunity, together with the suppression of adaptive immunity and associated inflammation.

Conclusions

It is almost thirty years since an interaction between vitamin D and the immune system was first documented. Although this was initially proposed as a non-classical effect of vitamin D associated with granulomatous diseases, our current view is now considerably changed. Recent studies have demonstrated a potential physiological role for vitamin D in regulating normal innate and adaptive immunity. Future studies will 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.

Acknowledgments

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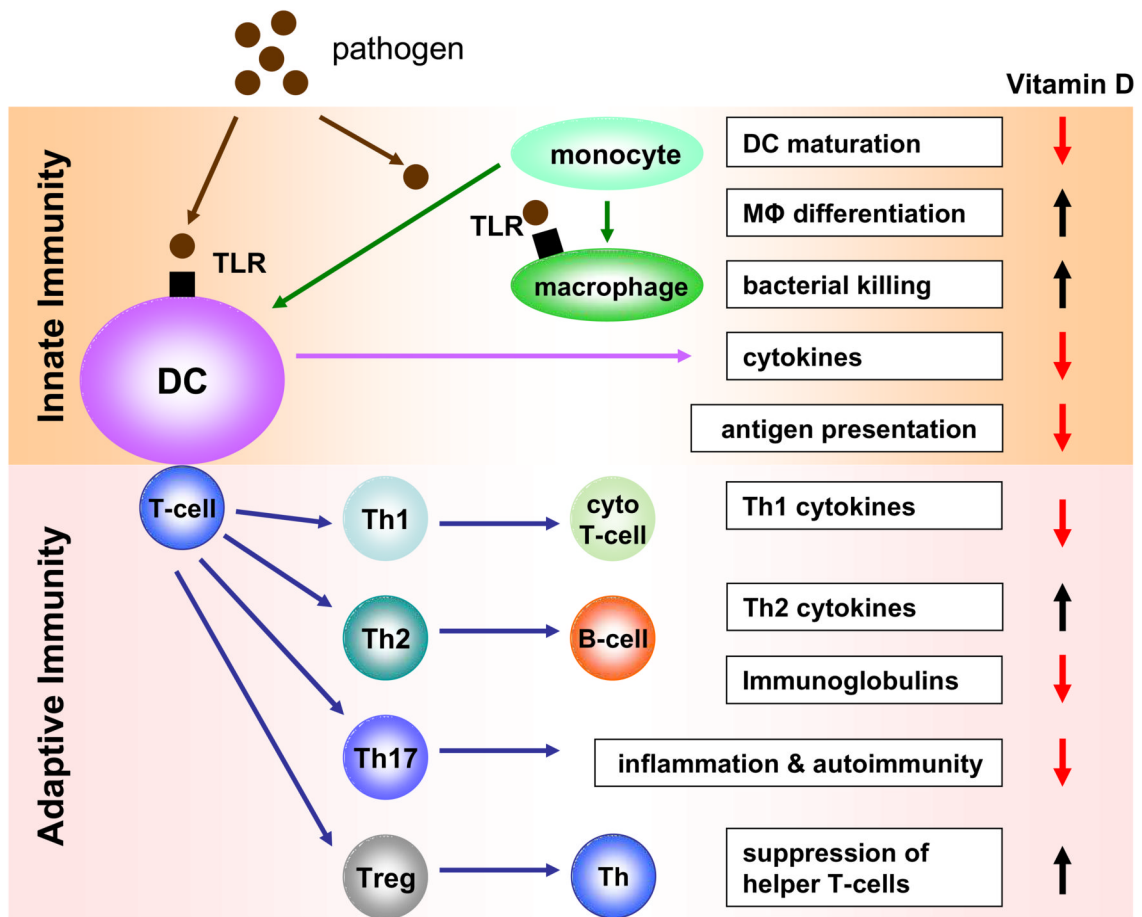
Figure 1. Effects of vitamin D on innate and adaptive immunity
Schematic representation of the principal innate and adaptive immune responses to a
pathogenic challenge, and the positive or negative regulation of these responses by vitamin D.
TLR, toll like receptor; DC, dendritic cell, Mφ, macrophage; T-cell, T-lymphocyte; cyto T-
cell, cytotoxic T-cell; B-cell, B-lymphocyte; Treg, regulatory T-cell.