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## Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity

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### Abstract

Vitamin D has received increased attention recently for its pleiotropic actions on many chronic diseases. The importance of vitamin D on the regulation of cells of the immune system has gained increased appreciation over the past decade with the discovery of the vitamin D receptor (VDR) and key vitamin D metabolizing enzymes expressed by cells of the immune system. Animal studies, early epidemiologic and clinical studies have supported a potential role for vitamin D in maintaining immune system balance. The hormonal form of vitamin D up-regulates anti-microbial peptides, namely cathelicidin, to enhance clearance of bacteria at various barrier sites and in immune cells. Vitamin D modulates the adaptive immune system by direct effects on T cell activation and on the phenotype and function of antigen-presenting cells (APCs), particularly of DCs. The purpose of this manuscript is to review the molecular and clinical evidence for vitamin D as a modulator of the innate and adaptive immune system.

### Keywords

Vitamins; Innate immunity; Immunology

### Introduction

Vitamin D has received increased attention recently for its pleiotropic actions on many chronic diseases including cancer, cardiovascular disease, autoimmune disease, diabetes, and neurologic disease [1]. It has been reported that vitamin D regulates over 900 genes [2]. The importance of vitamin D on the regulation of cells of the immune system has gained increased appreciation over the past decade with the discovery of the vitamin D receptor (VDR) and key vitamin D metabolizing enzymes expressed by cells of the immune system.

Animal studies, early epidemiologic and clinical studies have supported a potential role for vitamin D in maintaining immune system balance.

Vitamin D belongs to the family of steroid hormones and has its nuclear hormone receptor. Vitamin D has two major forms, cholecalciferol (vitamin D<sub>3</sub>) and ergocalciferol (vitamin D<sub>2</sub>). Both forms of vitamin D (D<sub>2</sub> and D<sub>3</sub>) can be found in foods or supplements; however, only vitamin D<sub>3</sub> is produced in skin. Pre-vitamin D<sub>3</sub> is formed from 7-dehydrocholesterol (also known as pro-vitamin D<sub>3</sub>) in skin upon exposure to ultraviolet B (UVB) radiation between the wavelengths of 290–315 nm. Pre-vitamin D<sub>3</sub> rapidly undergoes a thermally induced isomerization to form vitamin D<sub>3</sub>. Further exposure of pre-vitamin D<sub>3</sub> to UVB results in the formation of inactive vitamin D compounds which serves as a protective mechanism against vitamin D toxicity. Vitamin D<sub>3</sub>, that is formed in the skin, then enters the circulation bound to vitamin D binding protein where it undergoes a hydroxylation in the 25-position by the liver vitamin D-25-hydroxylase and in the 1-position by the kidney 25-hydroxyvitamin D-1-alpha-hydroxylase (1 $\alpha$ -OHase) to form 1,25(OH)<sub>2</sub>D (Fig. 1). The hormonal form of vitamin D enters the target cell from the circulation and binds to the vitamin D receptor (VDR) in the cytoplasm which then enters the nucleus and heterodimerizes with the retinoid X receptor (RXR). The 1,25(OH)<sub>2</sub>D-RXR-VDR complex then binds to vitamin D response elements (VDRE) located on DNA.

The classic function of vitamin D is to enhance intestinal absorption of calcium by regulating several calcium transport proteins in the small intestine. However, other cells including cells of the immune system possess the 1 $\alpha$ -OHase and VDR and thus are able to produce the hormonal form of vitamin D from circulating 25(OH)D and respond in an autocrine or paracrine fashion to form 1,25(OH)<sub>2</sub>D. It is important to note that the extra-renal 1 $\alpha$ -hydroxylase is regulated differently in response to PTH, calcium and phosphorus than the renal 1 $\alpha$ -hydroxylase [3]. In particular, the extra-renal 1 $\alpha$ -hydroxylase is not up-regulated by PTH and thus production of 1,25(OH)<sub>2</sub>D is dependent on concentrations of the substrate 25(OH)D [4].

Recent evidence demonstrates that macrophages produce the anti-microbial peptide LL-37 in response to endogenously produced 1,25(OH)<sub>2</sub>D to enhance innate immunity. Additional evidence shows 1,25(OH)<sub>2</sub>D modulates the adaptive immune system as well through direct effects on T cell activation and on the phenotype and function of antigen-presenting cells (APCs), particularly of DCs. The purpose of this manuscript is to review the molecular actions of vitamin D in several aspects of the immune system with particular focus on the innate immune system and the adaptive immune system as it relates to autoimmune disease.

## The role of vitamin D in the innate immune system

### Historical background

The use of vitamin D as a treatment of infections has been practiced for over 150 years. In 1849, Williams reported favorable results with use of cod-liver oil, an excellent source of vitamin D<sub>3</sub>, in the treatment of over 400 patients with tuberculosis (TB) [5]. Williams commented that the cod-liver oil was a “highly nutrient material” and had properties superior to other oils. Fifty years later, Niels Finsen, received the third Nobel Prize in Medicine for his description of using UV light, an effective method to increase vitamin D status, to treat lupus vulgaris, a cutaneous form of TB, in over 800 patients [6]. A popular belief at the time was that UV light directly killed *M. tuberculosis* [7]. The use of cod-liver oil and UV light for the treatment of TB became widely used during the early 1900s. Following the discovery of the chemical structures of vitamin D<sub>2</sub> and vitamin D<sub>3</sub>, found in cod-liver oil, by Nobel Laureate Alfred Windaus, several groups used vitamins D<sub>2</sub> and D<sub>3</sub> as a treatment for TB as reviewed by Martineau [8]. The introduction of more effective anti-TB

therapy and the unidentified mechanism of vitamin D action led to decreased use and interest in vitamin D therapy against TB infection in the mid 1900s. In the 1980s, Rook et al. demonstrated that  $1,25(\text{OH})_2\text{D}_3$  inhibited the proliferation of *M. tuberculosis* in culture; however, the mechanism still remained obscure [9]. As reviewed below, it is currently believed that vitamin D enhances innate immunity by up-regulating anti-microbial peptides such as cathelicidin in response to infection [10].

### Vitamin D and anti-microbial peptides

The innate immune system serves as the first barrier of defense against invading microorganisms such as bacteria, viruses, protozoa, and fungi [11]. The first task of the innate immune system is to recognize foreign organisms and to trigger a cascade of events that ultimately result in the removal and/or destruction of the invading organism. Pattern recognition receptors are expressed by cells of the innate immune system to recognize molecular patterns that are conserved among different classes of pathogens. These conserved patterns are termed pathogen-associated molecular patterns (PAMPs) [12]. Examples of PAMPs include lipopolysaccharide (LPS), flagellin, viral proteins and single- and double-stranded RNA. Toll-like receptors (TLRs) are a sub-class of pattern recognition receptors that are expressed primarily on the cell membrane or on endosomes [11]. The innate immune system response depends on the specific TLR and/or combination of TLRs that are triggered by PAMPs. The response to TLR signaling includes the production of anti-microbial peptides and cytokines and apoptosis of the host cells among other responses [12]. There are three major families of anti-microbial peptides in humans: cathelicidin, and  $\alpha$ - and  $\beta$ -defensins.

Humans have only one cathelicidin, hCAP18, which is cleaved to form LL-37 [13]. Cells of the immune system including neutrophils and macrophages and cells lining epithelial surfaces that are constantly exposed to potential pathogens such as the skin [14], respiratory tract [15], and gastrointestinal tract [16] produce cathelicidin. Cathelicidin has broad anti-microbial activity against gram-positive and -negative bacteria, as well as certain viruses and fungi [13]. The killing mechanism of cathelicidin involves bacterial lysis through membrane destabilization [17]. Humans with deficient cathelicidin production and cathelicidin knock-out mice are prone to infections of epithelial surfaces such as the skin and mucosal membranes. Therefore, anti-microbial peptides such as cathelicidin constitute an integral part of the innate immune response to a variety of infections especially at barrier sites.

Wang et al. provided one of the earliest studies that suggested that vitamin D could up-regulate the production of anti-microbial peptides [18]. They demonstrated that  $1,25(\text{OH})_2\text{D}_3$  treatment up-regulated cathelicidin mRNA in several cell lines and primary cultures including keratinocytes, neutrophils, and macrophages [18]. Furthermore, they reported the presence of the vitamin D response element (VDRE) on the promoter of genes coding the anti-microbial peptides cathelicidin and  $\beta$ -defensin [18]. Active vitamin D was able to induce cathelicidin mRNA in all cell lines tested whereas in contrast  $\beta$ -defensin was inducible only in primary keratinocytes and in lung adenocarcinoma cells [18]. The presence of the VDRE in the cathelicidin gene promoter is highly conserved in humans and primates and not present in non-primate animals, suggesting an important recent adaptation in evolution [19]. Gombart et al. have also confirmed that  $1,25(\text{OH})_2\text{D}_3$  up-regulates cathelicidin expression in several other human cell lines and primary cultures including those derived from skin, macrophages, neutrophils, lung, and colon [20,21]. Taken together, these findings suggest that  $1,25(\text{OH})_2\text{D}_3$  up-regulates anti-microbial peptide production, primarily cathelicidin, on a variety of different cells.

More recently, Liu et al. demonstrated that toll-like receptor stimulation with TLR2/1L of human macrophages resulted in up-regulation of the vitamin D receptor (VDR) and 25-

hydroxyvitamin D-1-alpha-hydroxylase ( $1\alpha$ -OHase or CYP27B1), the enzyme responsible for the conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D [10]. Furthermore, 1,25(OH)<sub>2</sub>D<sub>3</sub> up-regulated expression of cathelicidin mRNA in the presence of TLR2/1 L stimulation of human macrophage cultures. In cell viability assays of macrophages infected with *M. tuberculosis*, increasing concentrations of cathelicidin resulted in killing of intra-cellular *M. tuberculosis* [10]. When human sera from vitamin-D-deficient African-American subjects were added to human macrophage cultures stimulated by TLR2/1, no up-regulation of cathelicidin was detected; however, supplementation of the sera with 25(OH)D restored the cathelicidin response [10]. Therefore, the investigators propose a model in which *M. tuberculosis* triggering of toll-like receptors results in up-regulation of the vitamin D machinery, namely the VDR and the  $1\alpha$ -OHase, which leads to enhanced cathelicidin production *only* in the presence of adequate vitamin D status [10]. A similar reaction occurs in skin in response to injury. When skin is injured, there is up-regulation of CYP27B1 and cathelicidin [22]. In the presence of low 25(OH)D substrate or when either the VDR or CYP27B1 is inhibited in vitro, there is no longer up-regulation of cathelicidin. These studies indicate that 25(OH)D, the major form circulating form of vitamin D to determine vitamin D status, is important for local production of the hormonal form of vitamin D, 1,25(OH)<sub>2</sub>D, to up-regulate cathelicidin production in skin and in macrophages. Since keratinocytes also possess the 25-hydroxylase, UV light may directly stimulate cathelicidin production by providing the substrate 25(OH)D directly from cutaneously produced vitamin D<sub>3</sub> [23].

### Epidemiologic and clinical associations between vitamin D status and infection

A number of epidemiologic studies using vitamin D status or season as the exposure have found an inverse association between vitamin D and incidence of several infections, including influenza [24], upper respiratory tract infection [25–27], HIV infection [28], and bacterial vaginosis [29]. Recent cross-sectional studies have attempted to determine whether vitamin D status was associated with serum levels of cathelicidin. Jeng et al. examined a cohort of critically ill patients with and without sepsis and healthy controls and found a weak but statistically significant positive association between serum 25(OH)D and LL-37 [30]. Gombart et al. found that serum hCAP18 was associated with increased mortality from infection in patients with end-stage renal disease [31]. They did not find an association between 25(OH)D and hCAP18 likely due to the finding that 80% of the subjects had vitamin D insufficiency; however, there was a borderline ( $p=0.053$ ) association between serum 1,25(OH)<sub>2</sub>D and hCAP18 [31].

Several randomized controlled trials have been conducted to examine whether vitamin D supplementation would reduce the risk of disease from viral, bacterial, fungal and protozoan infections [32]. However, given the heterogeneity in the dose, sample population, and duration of vitamin D therapy of the trials reviewed, there was insufficient data to conclusively state that vitamin D supplementation could result in lowered infection rate [32]. A meta-analysis comparing 25(OH)D concentrations in TB-infected subjects to healthy controls found a higher risk of vitamin D deficiency in TB-infected subjects [33]. Recent studies have been inadequate in dosing of vitamin D, including a large randomized controlled trial of TB-infected patients where both control and vitamin D treatment groups had similar 25(OH)D concentrations at the end of the study [34]. To determine whether vitamin D supplementation could raise cathelicidin levels in humans, Adams et al. gave osteoporotic women 50,000 IU of vitamin D<sub>2</sub> twice weekly for 5 weeks and found no change in serum cathelicidin levels; however, cathelicidin mRNA expression in peripheral blood monocytes was increased after high-dose vitamin D supplementation [35]. Larger doses and more rapid dosing of vitamin D are likely required to up-regulate cathelicidin expression in response to infection in humans [36]. Furthermore, levels of cathelicidin are

likely to be induced in barrier sites as opposed to in the systemic circulation for localized infections.

### Vitamin D, innate immunity, and evolution

Several investigators have proposed that as early man migrated from the equator to higher latitudes, there was a selection pressure to de-pigment skin to maximize cutaneous production of vitamin D [37,38]. Vitamin D deficiency leads to a rachitic pelvis increasing the risk of death in childbirth [39]. The discovery of a *Homo erectus* skull in Western Turkey with the earliest reported findings of TB infection in a hominin fossil lead the authors to speculate that reduced UV radiation leading to vitamin D deficiency resulted in increased susceptibility to TB infection, presenting another challenge to Northward migration [40]. Could vitamin D regulation of the innate immune system in primates be another adaptation to counteract susceptibility to infection? Because bacteria have increased mutagenesis in the presence of UV radiation, it may be that the regulation of anti-microbial peptides by vitamin D is a counter evolutionary response to increased bacterial resistance [41].

### The role of vitamin D in autoimmune disease

#### Background

Although the natural history of autoimmunity remains largely unknown, the widespread theory is that both genetic susceptibility and environmental factors play a role in the development of clinical disease. Both experimental observations and clinical studies suggest a key role for vitamin D as a modifiable environmental factor in autoimmune disease (Fig. 2) [42]. Vitamin D has known immunomodulatory effects on a wide range of immune cells, including T lymphocytes, B lymphocytes, and dendritic cells [43,44]. Each of these immune cell types express VDR and produce the enzymes  $1\alpha$ -OHase and 24-hydroxylase, and are therefore capable of locally producing active  $1,25(\text{OH})_2\text{D}$  [45–49]. The autocrine and paracrine functions of  $1,25(\text{OH})_2\text{D}$  are under tight immune system regulation and are dependent on an adequate supply of circulating  $25(\text{OH})\text{D}$ , making the epidemic of vitamin D deficiency critical to address for immune system health.

#### Specific effects on T and B cells

Activation of CD4+ T cells results in a fivefold increase in VDR expression, enabling regulation of at least 102 identified genes responsive to  $1,25(\text{OH})_2\text{D}$  [50].  $1,25(\text{OH})_2\text{D}$  suppresses T cell receptor induced T cell proliferation and alters their cytokine expression profile [46,51]. The overall shift is away from a T helper (Th)1 phenotype toward a more tolerogenic Th2 phenotype [52,53].  $\text{IFN}\gamma$  and IL-2 production by T cells are diminished by exposure to  $1,25(\text{OH})_2\text{D}$  while IL-5 and IL-10 are increased, consistent with a shift towards a Th2 response [54,55]. The production of the Th2 cytokine IL-4 is up-regulated by  $1,25(\text{OH})_2\text{D}$  in most, but not all, studies [54,56]. Vitamin D appears to directly inhibit Th1 cells and may additionally modulate a skewing towards a Th2 response by its inhibitory effects upon IL-12 [57].

Th17 cells are a subset of CD4+ T cells involved in organ-specific autoimmunity, playing a role in maintaining inflammation which can lead to tissue damage [58]. In animal models of autoimmune uveitis [59] and inflammatory bowel disease [60],  $1,25(\text{OH})_2\text{D}$  suppresses autoimmunity and tissue destruction by inhibiting the Th17 response at several levels, including the ability of dendritic cells to support priming of Th17 cells and the ability of Th17 cells to produce IL-17. Vitamin D inhibits the expression of IL-6 [61,62], a cytokine which stimulates Th17 cell genesis, and suppresses IL-12p70, IL-23p19, and further IL-6 and IL-17 expression [60]. In addition to effects on CD4+ cells, vitamin D facilitates the

induction of Foxp3+ T regulatory cells [57,63] and there is a positive correlation between serum 25(OH)D levels and the ability of T regulatory cells to suppress T cell proliferation [64]. Altogether, the evidence supports an important role for vitamin D in influencing T cell responses and in tempering inflammation and tissue damage.

Vitamin D has a direct effect on B cells and inhibits immunoglobulin production [65]. Furthermore, when exposed in vitro to 1,25(OH)<sub>2</sub>D, differentiation of B lymphocytes is interrupted [47]. Peripheral blood mononuclear cells (PBMCs) from patients with SLE are sensitive to the effects of vitamin D; addition of 1,25(OH)<sub>2</sub>D to SLE PBMCs results in significant reduction of both spontaneous polyclonal antibody production and pathogenic anti-dsDNA autoantibody production by SLE B cells [66].

### Effects on dendritic cells

Perhaps the most profound effects of 1,25(OH)<sub>2</sub>D on the immune system, and of high relevance to autoimmunity, are the effects on dendritic cells (DCs) [67,68]. DCs have important functions in maintaining both protective immunity and self-tolerance [69,70]: immature DCs promote T cell tolerance, whereas mature DCs activate naïve T cells. Mechanisms of action of 1,25(OH)<sub>2</sub>D on DCs include actions on the differentiation of monocytes into immature DCs, the maturation of DCs, and DC survival [67,71–74]. Overall, 1,25(OH)<sub>2</sub>D leads to the development of DCs with tolerogenic properties. Expression of VDR increases rapidly as monocytes develop into monocyte-derived DCs (MDDCs) [68]. Physiologic levels of 1,25(OH)<sub>2</sub>D inhibit maturation of DCs, and maintain an immature and tolerogenic phenotype with inhibition of activation markers such as MHC class II, CD40, CD80, and CD86 and up-regulation of inhibitory molecules (ILT3) [57,67]. Furthermore, 1,25(OH)<sub>2</sub>D down-regulates IL-12 and augments IL-10 production by DCs, promoting a shift from a Th1 to a Th2 phenotype [57]. MDDCs that have developed in the presence of 1,25(OH)<sub>2</sub>D exhibit less IL-12p40 in response to LPS (a maturation trigger for immature DCs) and are less responsive to inflammatory chemokines that regulate DC migration to lymph nodes [72]. Since the maturational state of DCs can be modulated by 1,25(OH)<sub>2</sub>D, the vitamin D status of an individual is likely to have important immunologic consequences.

### Vitamin D and autoimmune disease

There have been several animal models of autoimmunity in which disease could either be prevented or ameliorated with the administration of either 1,25(OH)<sub>2</sub>D<sub>3</sub> or one of its analogues. These animal models include autoimmune encephalomyelitis (EAE), collagen-induced arthritis, type-1 diabetes mellitus, inflammatory bowel disease, autoimmune uveitis, and lupus [43,59,75–86]. These studies demonstrate that treatment with hormonally active vitamin D is effective in modulating immune function and positively impacting autoimmune disease.

Vitamin D deficiency is a risk factor for development of a number of autoimmune diseases. Many of the clinical studies assess vitamin D status using dietary questionnaires, which is an inadequate surrogate without taking sun exposure and skin pigmentation into account [87]. This is especially true in later studies as increased awareness of skin cancer has resulted in greater general use of sunscreen and sun avoidance. These methodological limitations can explain some of the inconsistent results seen in large epidemiologic studies of vitamin D intake on the incidence of rheumatoid arthritis (RA). The Iowa Women's Health Study, a population-based cohort of 41,837 post-menopausal women, found a significantly higher risk of developing RA in women reporting a lower intake of vitamin D at baseline [88]. These findings could not be replicated using similar methods in a different cohort (Nurses' Health Study) [89]. Studies utilizing 25(OH)D levels include a report from Amsterdam that found no significant difference in 25(OH)D levels at three time points (1, 2, and ≥5 years

prior to symptom onset) between 79 patients who subsequently developed RA and 79 age-, sex-, and season-matched controls [87]. However, other studies show that low levels of 25(OH)D contributes to disease activity and inflammation among those with established inflammatory arthritis [90] and RA [91].

The findings linking vitamin D deficiency to multiple sclerosis (MS), type 1 diabetes (T1DM), and systemic lupus erythematosus (SLE) are more consistent. A reduced risk of developing MS with vitamin D supplementation of  $\geq 400$  IU/day compared to no supplementation was documented in two large observational cohorts of women from the Nurses' Health Study (RR 0.59,  $p$  for trend=0.006) [92]. Confirmation of these associations was made using the Department of Defense Serum Repository of 7 million US military personnel [93]. Among whites, the OR of developing MS was 0.59 (95% CI 0.36–0.97) with increasing levels of 25(OH)D; OR was 0.38 (95% CI 0.19–0.75) for the highest quintile of 25(OH)D [93]. Studies also suggest that disease activity measured in active MRI brain lesions and relapse rates in MS increase during seasonal periods of lower circulating 25(OH)D and decrease during periods of higher 25(OH)D [94–96].

### Vitamin D status and type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM), one of the most prevalent chronic diseases with onset in childhood, results from an immune-mediated destruction of pancreatic insulin-producing  $\beta$ -cells. There is a marked geographic variation in incidence following a latitudinal gradient that is the inverse of the global distribution of ultraviolet B (UVB) irradiance [97].

One of the environmental factors thought to be protective against the development of T1DM is early supplementation with vitamin D. Four large case-control studies were included in a meta-analysis showing that the risk of T1DM was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented (pooled odds ratio 0.71, 95% CI 0.60 to 0.84) [97]. There also was evidence of a dose–response effect, with those using higher amounts of vitamin D being at lower risk of developing T1DM [97].

A birth cohort study in Finland, now more than 40 years ago, evaluated the effects of vitamin D supplementation on rickets and the subsequent development of T1DM [98]. All women due to give birth in 1966 were enrolled (12,058 live births). There were 10,366 children analyzed, of whom 81 developed T1DM. There was an approximately 80% reduction in the risk of T1DM in children receiving  $\geq 2000$  IU vitamin D/day, compared to those receiving less (adjusted RR 0.22; 95% CI 0.05, 0.89), which is in agreement with the meta-analysis of case-control studies [97]. Evidence from both human and animal studies show that vitamin D plays an important role in T1DM, and early intervention with supplemental vitamin D appears to offer protection from its development.

### Vitamin D status and SLE

Type I interferons play an important role in SLE and the up-regulation of IFN $\alpha$  inducible genes, termed the “interferon signature,” is seen in approximately 50% of patients with SLE and correlates with disease activity [99,100]. Plasmacytoid DCs, responsible for this signature, release IFN $\alpha$  after stimulation by nucleic acid-containing immune complexes. SLE plasma is capable of inducing/transferring the interferon signature to normal, non-autoimmune PBMCs. Observations that 1,25(OH) $_2$ D $_3$  inhibits in vitro dendritic cell maturation/activation and type I interferon production are of interest and suggest that giving vitamin D as a therapeutic intervention may be beneficial in SLE [42,73,101].

Several methods have been used to examine potential links between vitamin D status and SLE, including case-control, cohort, and retrospective observational studies, using serum 25(OH)D levels and dietary intake of vitamin D as a surrogate marker of vitamin D status

[102]. SLE cases have lower 25(OH)D levels compared to controls, suggesting that vitamin D deficiency may be a risk factor for SLE [103–105]. However, findings from the Nurse's Health Study I and II prospective cohorts showed no association between vitamin D intake and development of SLE [106]. As mentioned previously, this study was limited by the use of intake questionnaires which are an inadequate surrogate for serum 25(OH)D levels. The majority of studies have also found higher SLE disease activity associated with lower levels of serum 25(OH)D [102]. Because patients with SLE often have photosensitivity and are advised to avoid direct sun exposure, detecting and replacing 25(OH)D deficiency with oral supplementation is even more critical.

## Optimal levels of 25-hydroxyvitamin D

It is clear that 1,25(OH)<sub>2</sub>D has physiologic effects beyond that of bone and mineral homeostasis and that the alarming prevalence of vitamin D deficiency seen worldwide may be contributing to immune-mediated diseases. Based on bone-related biomarkers such as intact parathyroid hormone, calcium absorption and bone mineral density, maintaining a 25(OH)D level of at least 32 ng/ml appears sufficient. The prospective studies needed to test whether similar levels are necessary for optimal immune health have not yet been completed. Potentially higher cutoffs of 25(OH)D will be needed and a better understanding will likely be available in the near future as research progresses.

## Conclusions

### Innate and adaptive immune balance

Potent immunomodulatory activities of vitamin D on both innate and adaptive immune responses have been recently discovered [12,22,25,99,107–114]. While innate immunity is enhanced against “high-affinity” foreign antigens, vitamin D sufficiency has a dampening effect on the processing of “low-affinity” self antigens. Although the precise mechanisms are still being discovered, the important role of vitamin D in maintaining immune homeostasis should not be overlooked. Interventional studies to further define the immunomodulatory effects of vitamin D in humans need to be done.

In summary, the effects of 1,25(OH)<sub>2</sub>D on the immune system include decreasing Th1/Th17 CD4<sup>+</sup> T cells and cytokines, increasing regulatory T cells, downregulation of T cell-driven IgG production and inhibition of dendritic cell differentiation. While enhancing protective innate immune responses, 1,25(OH)<sub>2</sub>D helps maintain self-tolerance by dampening overly zealous adaptive immune responses [115].

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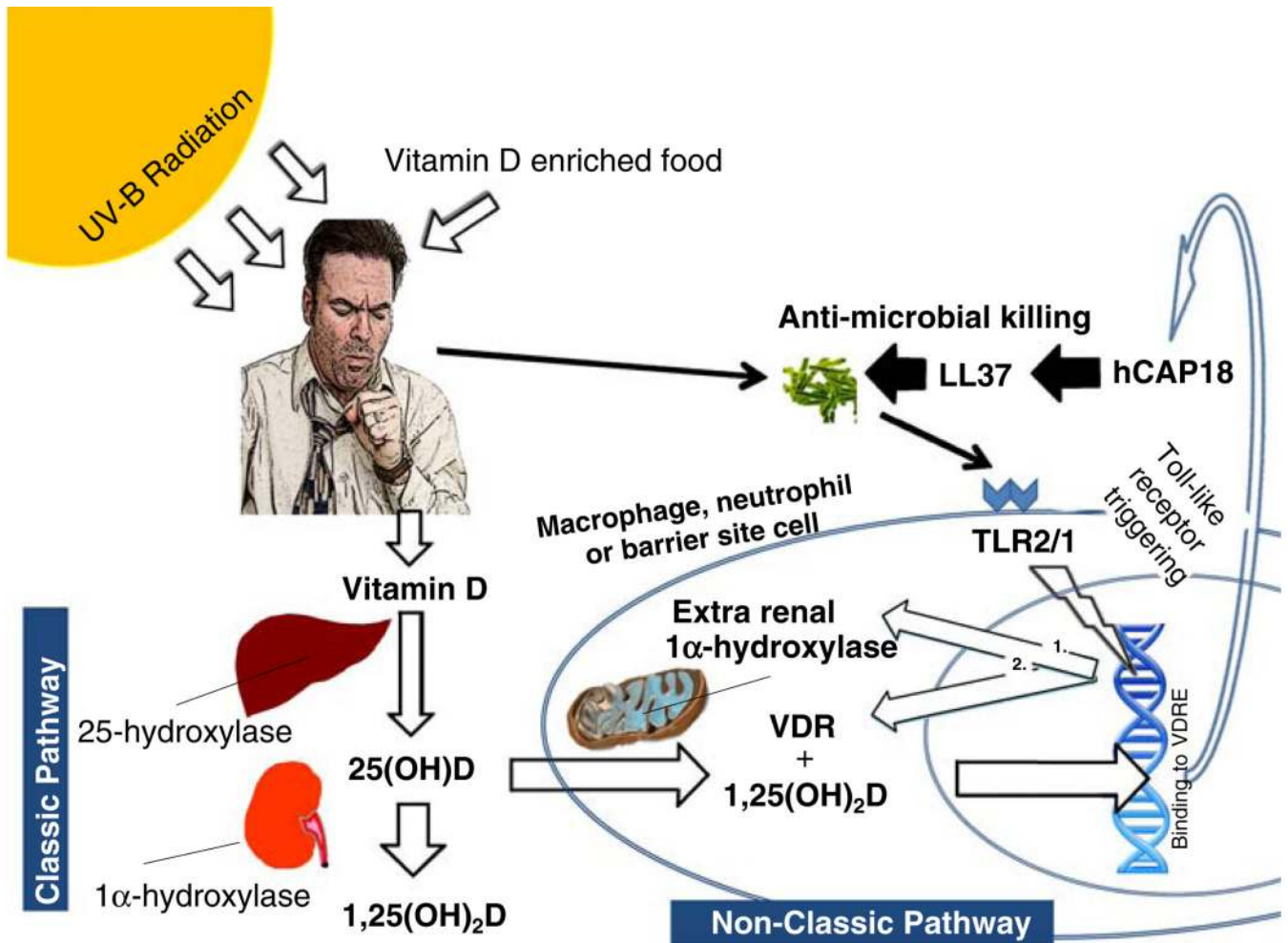
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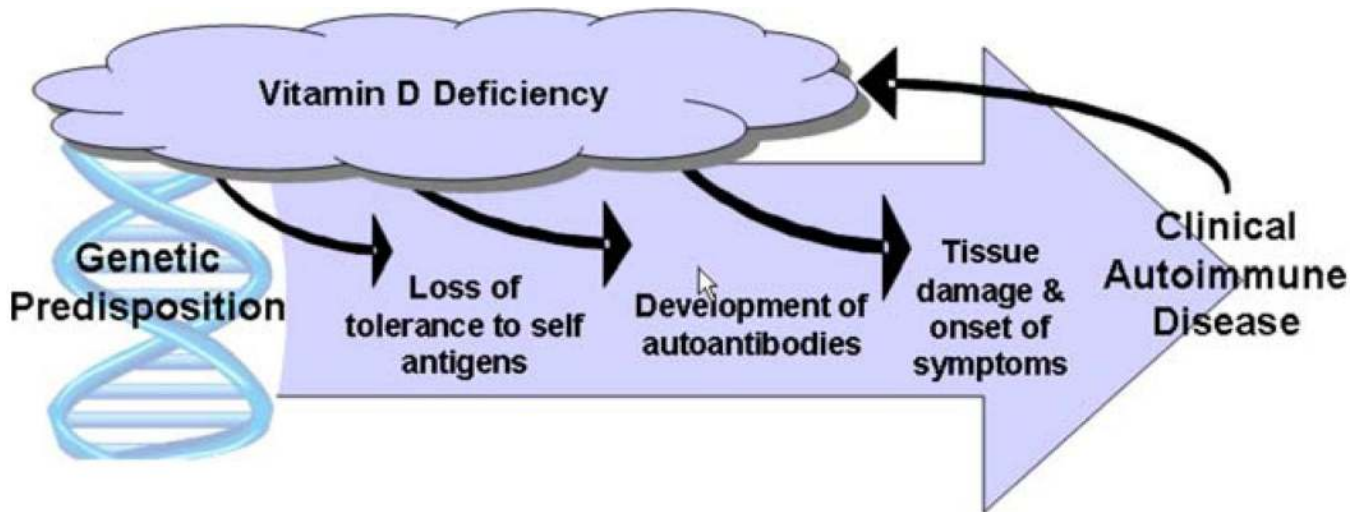
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**Fig. 1.**

Proposed mechanism for vitamin D's action on the innate immune system. Vitamin D is produced in the skin upon exposure to UVB radiation from the sun or obtained from vitamin D containing foods. Vitamin D is converted to its major circulating form, 25-hydroxyvitamin D (25(OH)D), by the liver 25-hydroxylase and to 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) by the kidney 1-α-hydroxylase for optimal intestinal absorption of calcium in the classic vitamin D pathway. In the non-classic pathway of the immune system, the circulating 25(OH)D is taken up by macrophages, neutrophils or epithelial cells at locations exposed to the external environment. The 25(OH)D is converted to 1,25(OH)<sub>2</sub>D in the target cell to act as an autocrine hormone. The locally produced 1,25(OH)<sub>2</sub>D binds to its nuclear receptor (VDR) and binds to the promoter of genes containing the vitamin D response element (VDRE). In neutrophils, macrophages and epithelial cells, this results in increased production of uncleaved cathelicidin (hCAP18 in humans) which undergoes further cleavage to the active cathelicidin (LL37 in humans) which results in killing of microorganisms. Of note, invading microorganisms that trigger specific toll-like receptors (in this example, TLR 2/1) result in increased production of the VDR and 1-α-hydroxylase which allows for vitamin D to enhance the production of cathelicidin only in the presence of adequate 25(OH)D substrate (adapted from Ref. [8])



**Fig. 2.**

Proposed mechanism for vitamin D's influence on the development and progression of autoimmunity.  $1,25(\text{OH})_2\text{D}$  regulates DC maturation and the differentiation and activity of  $\text{CD4}^+$  T cells to prevent the loss of self-tolerance. In a genetically predisposed individual, it is more likely that autoantibodies will develop and proliferate in the setting of vitamin D deficiency. Ultimately, deficiency of vitamin D may act as an environmental trigger of clinical disease. Left untreated, the cycle of vitamin D deficiency will continue as many autoimmune diseases and several medications used to treat them lead to sun avoidance from photosensitivity. The role of vitamin D status in the natural history of autoimmunity warrants further investigation