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MINIREVIEW

Vitamin D Signaling, Infectious Diseases, and Regulation of Innate Immunity▽

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Vitamin D was first identified as a cure for nutritional rickets, a disease of bone growth caused by an inadequate uptake of dietary calcium. It is now known that vitamin D can be obtained through two independent pathways: limited dietary sources and the photochemical action of solar UV light in the skin. Cod liver oil was discovered to be an excellent source of antirachitic activity in 1827, although it was not until several decades later that the active ingredient was identified as vitamin D_3. Even earlier, in 1822, a Polish physician studying children reached the remarkable conclusion that sunlight cured rickets after noting that rickets was relatively rare in the clearer air of rural areas. Almost 100 years later, in 1919, it was shown that artificial UV light cured rickets (49; www.beyonddiscovery.org/Includes/DBLink.asp?ID=1176). Indeed, secosteroidal vitamin D_3 is produced in the skin via photochemical and thermal conversion of 7-dehydrocholesterol in the presence of UVB light (~295 to 320 nm). While it seems that vitamin D is readily accessible via dietary or solar routes, vitamin D insufficiency or deficiency is, in fact, quite widespread. Solar UVB irradiation is absorbed by atmospheric ozone; consequently, the surface intensity of UVB varies markedly with latitude and time of year. Moreover, as vitamin D intake is generally inadequate in most diets (38–40), the rate of vitamin D insufficiency or deficiency increases with increasing latitude.

The term vitamin D refers collectively to vitamin D_3 and vitamin D_2, which is derived from irradiation of the steroid ergosterol in yeast. Biologically active vitamin D is generated via largely hepatic 25-hydroxylation catalyzed by CYP2R1, CYP27A1, and possibly other enzymes to produce 25-hydroxvitamin D (25D) (21, 40, 43, 67, 81), which has a long half-life and is the major circulating vitamin D metabolite. 25D is modified by 1α-hydroxylation catalyzed by CYP27B1, which produces hormonal 1,25-dihydroxyvitamin D (1,25D) (40, 43, 67). Vitamin D compounds are catabolized via 24-hydroxylation by CYP24, whose expression is strongly inducible by 1,25D, which constitutes a negative feedback loop (40, 43, 67).

While the kidneys are a major site of 1α-hydroxylation of 25D, it has recently become clear that generation of hormonal 1,25D in peripheral tissues is critical to the full scope of the physiological actions of this compound. Renal 1α-hydroxylation is tightly controlled by calcium homeostatic signals, particularly circulating parathyroid hormone (PTH). Although initially characterized as a calcium homeostatic agent, vitamin D is now known to have pleiotropic actions, including a key role in immune system regulation (49). Importantly in this regard, recent research detailed here has uncovered critical, cell-specific differences in both the regulation of 1α-hydroxylation of 25D and 24-hydroxylation that are relevant to the role of 1,25D as an immune system regulator.

VITAMIN D INSUFFICIENCY/DEFICIENCY AND DISEASE

While there is no strict definition, vitamin D deficiency is widely defined as circulating 25D levels of less than 20 ng/ml (50 nM) (11, 39, 40, 53, 87), whereas an individual is generally considered to be vitamin D sufficient if the circulating 25D concentration is greater than 30 to 32 ng/ml (75 to 80 nM) (19, 37, 87). 25D levels are inversely associated with circulating PTH levels until the 25D concentration is greater than 30 to 40 ng/ml, at which point PTH levels bottom out. While vitamin D intoxication can occur, it is not observed until 25D levels reach 150 ng/ml (375 nM) or more (40), and it is associated with hypercalcemia, which, if chronic, can result in urinary calculi (renal or bladder stones) and renal failure.

While cases of vitamin D toxicity do occur, vitamin D insufficiency/deficiency is far more common. In temperate regions, surface solar UVB irradiation is insufficient to induce cutaneous vitamin D_3 synthesis for periods around the winter solstice that are up to 6 months long or longer at higher latitudes (38), a period that is known as vitamin D winter. For obvious reasons, cutaneous vitamin D synthesis is also strongly influenced by skin color (55). Lack of cutaneous vitamin D synthesis, coupled with vitamin D-poor diets, has contributed to high levels of vitamin D insufficiency or deficiency in European and North American populations (38–40, 60). For example, a survey of healthy females across northern Europe found that there was widespread vitamin D deficiency (6), and a recent study found that 42% of African-American women in the United States were seriously 25D deficient (<15 ng/ml) (19).

Epidemiological studies have linked vitamin D deficiency to increased rates of cancer, as well as autoimmune and infectious diseases (80). In the United States the rates of bladder, breast, colon, ovary, and rectal cancer increase twofold from south to north (34). North-south gradients of autoimmune conditions, such as multiple sclerosis, Crohn's disease, and type 1 diabetes,

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have also been documented (2, 15, 47, 59). Connections between vitamin D insufficiency and infectious diseases go back over 100 years to the recognition in the 19th century that solar radiation was beneficial for patients suffering from tuberculosis (TB). Associations between vitamin D deficiency and TB susceptibility were described over 20 years ago (22, 33). A more recent study of a genetically homogeneous immigrant population of Gujarati Asians in the London area with high rates of TB found that there was an association between active disease and 25D deficiency and that there was an even stronger association of disease with undetectable serum levels of 25D (101). In addition, we have known for over 20 years that 1,25D inhibits the growth of *Mycobacterium tuberculosis* in cultured human macrophages (73). Interest in the connection between vitamin D supplementation and treatment of TB has been rekindled lately by the findings of several studies (50–52, 54, 75), not least of which was the recent observation of Martineau and colleagues in a double-blind randomized controlled trial that a single dose of 100,000 U (2.5 mg) of vitamin D_3 enhanced antimycobacterial immunity in healthy tuberculin skin test-positive donors (54). In addition, critical links described below have recently been made between molecular events controlling vitamin D signaling pathways and innate immune responses against mycobacterial infection.

While the potential protective effects against TB infection have attracted the most attention, data are accumulating from several sources that vitamin D may also be beneficial in combating a range of other bacterial or viral infectious agents. One small but intriguing study worthy of follow up found that elderly women undergoing long-term treatment with vitamin D as an antiosteoporosis agent had a significantly lower rate of *Helicobacter pylori* infections than women in an untreated control group (44). There have also been a number of studies examining the potential role of vitamin D in protection against upper and lower respiratory tract infections, which can be caused by a variety of etiological agents, many of which are viral (14, 57, 102). Subclinical vitamin D deficiency was associated with severe lower respiratory tract infection in an Indian study (97), and clinical vitamin D deficiency was associated with a 13-fold-increased risk of pneumonia in Ethiopian children (58). A Finnish study found that there was an association between serum 25D concentrations of less than 40 nM (16 ng/ml) and a range of acute respiratory infections (sinusitis, tonsillitis, otitis, bronchitis, pneumonia, pharyngitis, and laryngitis) in young army recruits (46). In addition, Cannell and several colleagues have persuasively argued, based on a range of epidemiological data, that cutaneous vitamin D production provides the "seasonal stimulus" associated with solar radiation that underlies the seasonality of epidemic influenza (16, 17). Finally, clinical and genetic evidence is accumulating that vitamin D may play a role in modulating human immunodeficiency virus (HIV) infection, although more work needs to be done to clarify the relationship between vitamin D physiology and HIV infection. A positive correlation was established between vitamin D supplementation and CD4-positive T-cell counts in seropositive individuals (94). A correlation between mortality from HIV infection and vitamin D deficiency has not been clearly established. However, interpretation of the vitamin D status of HIV-positive individuals is complicated by the potential confounding effects of antiretroviral therapy on vitamin D metabolism (94). This is an area that merits further clarification, because, as detailed below, a potential role for 1,25D signaling in modulating HIV infection is supported by genetic studies on vitamin D receptor (VDR) gene polymorphisms.

VDR GENE POLYMORPHISMS AND INFECTIOUS DISEASES

The association between vitamin D physiology and infectious disease is also supported by genetic studies implicating polymorphisms in the gene encoding the VDR in disease susceptibility (91). There are numerous *VDR* polymorphisms, including a common *Fok1* restriction fragment length polymorphism (RFLP) that shifts translational initiation to an ATG three codons downstream and *Taq1* and *Bsm1* RFLPs in the 3′ untranslated region. Genetic studies have linked *VDR* polymorphisms with a number of infectious diseases, including susceptibility to *M. tuberculosis* infection and treatment outcome. A Peruvian study found an association between specific genotypes of both the *Taq1* and *Fok1* RFLPs and time to microbiologic resolution of pulmonary TB (75). In a case-control study of 2,015 African subjects, homozygotes for *Taq1* polymorphism (genotype *tt*) were significantly underrepresented in TB patients (8). In the study on Gujarati Asians mentioned above, the *ff* genotype of the *Fok1* RFLP was associated with the extent of pulmonary TB in 25D-deficient patients (101).

VDR polymorphisms have also been linked to leprosy, which is caused by a distinct mycobacterial agent, *Mycobacterium leprae* (29). Tuberculoid leprosy presents with few bacilli in macrophages and a strong cell-mediated response, whereas the more severe lepromatous leprosy is characterized by numerous bacilli and a weak cellular response. The *tt VDR* polymorphism was associated with tuberculoid leprosy in Bengali patients, whereas the *TT* genotype was associated with lepromatous leprosy (77). Although the *tt* genotype was associated with susceptibility to leprosy in a case-control study of patients in the Karonga district of Malawi (30), the expected frequency of *tt* homozygotes was low (5%), and apparent differences between patient and control populations could have been due to chance.

A recent analysis of young children found that the *ff* genotype was associated with adjusted relative odds of acute lower respiratory tract infection (predominantly viral bronchiolitis) that were seven times those of the *FF* genotype (76). VDR polymorphisms have been linked to HIV infection, although clear conclusions regarding the role of vitamin D signaling in controlling HIV infection have been difficult to draw. No associations were found between *Bsm1* polymorphisms and HIV infection, whereas an association was established between the *BB* genotype and disease progression based on several criteria (7). However, it is difficult to ascribe variations in the *Bsm1* genotype to changes in VDR function. Another recent study found no association between a specific polymorphism and protection against HIV infection in a population of injection drug users, but it did find a correlation between specific *VDR* haplotypes (blocks of polymorphisms) (23). The authors concluded that protective *VDR* polymorphisms were associated with reduced VDR function, consistent with vitamin D signal-

ing promoting HIV infection, and noted based on an in vitro study that the 1,25D-bound VDR could activate the HIV type 1 long terminal repeat (61).

MOLECULAR MECHANISMS OF ACTION OF VITAMIN D

Much of the action of 1,25D can be explained by its binding to and activation of the VDR. The VDR is a nuclear receptor and ligand-activated transcription factor (20, 49) composed of a highly conserved DNA binding domain and an α-helical ligand binding domain (72). The ligand-bound VDR activates transcription by heterodimerization with retinoid X receptors (RXRs), which is essential for high-affinity DNA binding to cognate vitamin D response elements (VDREs) located in the regulatory regions of 1,25D target genes. VDREs are composed of direct repeats of PuG(G/T)TCA motifs separated by 3 bp (DR3) or everted repeats with 6-bp spacing (ER6) (20, 26, 49, 89, 90). (Note that everted repeats are palindromic but have symmetry [toes pointing out] opposite that of the so-called inverted repeats [toes pointing in] originally identified as response elements for steroid receptors.) ER8 motifs can also function as response elements for the VDR and related retinoic acid receptors (86), thus partially integrating 1,25D and retinoid signaling. DNA-bound VDR/RXR heterodimers recruit numerous so-called coregulatory proteins, which control histone modifications, chromatin remodeling, and RNA polymerase II binding and transcriptional initiation (24, 31, 56, 70, 74). The ligand-bound VDR can also repress transcription. For example, in the presence of 1,25D, VDR/RXR heterodimers can displace DNA-bound nuclear factor of activated T cells, thus repressing cytokine gene expression (5, 85). While numerous VDREs have been identified in relatively promoter-proximal locations, recent work has provided evidence that the DNA-bound VDR can function at distances as great as 75 kb to regulate adjacent target gene transcription (45).

VITAMIN D SIGNALING AND METABOLISM IN THE IMMUNE SYSTEM

Evidence for a role of vitamin D signaling in the immune system in general and in innate immune responses in particular has been accumulating from a variety of sources. The VDR is present in most cells of the immune system, including T lymphocytes, neutrophils, and antigen-presenting cells, such as macrophages and dendritic cells (3, 10, 12, 62, 69). 1,25D is an inhibitor of maturation of dendritic cells, the most potent of the antigen-presenting cells, and acts directly on T lymphocytes to inhibit T-cell proliferation (92). 1,25D signaling represses the transcription of genes encoding key T helper 1 (Th1) cytokines, such as gamma interferon and interleukin-2 (5, 92). 1,25D is thus a suppressor of antigen presentation to and activation and recruitment of Th1 cells. The net effect of 1,25D action is to polarize T-helper responses toward a more regulatory Th2 phenotype, which is considered a key component of its capacity to suppress Th1-driven autoimmune responses (92).

In the last few years, researchers in the vitamin D field, and particularly researchers interested in the immunomodulatory functions of vitamin D, have come to appreciate the important contributions of extrarenal 1α-hydroxylase (CYP27B1) to vitamin D physiology. Activated macrophages and dendritic cells express CYP27B1 (1, 64, 65, 84), which, unlike the renal enzyme, is not regulated by Ca^{2+} homeostatic signals but is regulated primarily by immune inputs, mainly gamma interferon and agonists of the Toll-like receptor (TLR) pattern recognition receptors. Critically, this renders the immune system responsive to circulating levels of 25D. Liu and colleagues found in microarray studies that signaling through human macrophage TLR1/2 heterodimers stimulated with bacterial lipopeptides induced expression of both CYP27B1 and the VDR (50) (Fig. 1). Most importantly, they showed that in TLR2/1-stimulated human macrophages cultured in the presence of human serum, downstream VDR-driven responses were strongly dependent on serum 25D concentrations. VDR-driven responses were strongly attenuated or absent in serum from vitamin D-deficient individuals, a defect that could be overcome by 25D supplementation. Moreover, consistent with previous findings (60, 82), the 25D levels in serum from African-Americans used in the study were markedly lower than those of Caucasian Americans (50). This study thus provided a clear demonstration of the dependence of immune responses on circulating 25D levels. Similarly, stimulation of the TLR4/CD14 receptor complexes by lipopolysaccharide induces *CYP27B1* expression (84; unpublished results), consistent with correlations that other workers have found between TLR4 and CYP27B1 expression (27, 28).

Remarkably, while expression of CYP24, the mitochondrial enzyme that initiates 1,25D catabolism, is exquisitely sensitive to the presence of 1,25D, the negative feedback loop appears to be defective in macrophages (Fig. 1). Ren and colleagues have recently shown that while expression of *CYP24* transcripts is induced by 1,25D in macrophages as in other cells, the corresponding enzymatic activity is virtually undetectable (71). 1,25D induces the expression in macrophages of a splice variant form (CYP24-SV) that encodes a truncated enzyme lacking the critical amino-terminal mitochondrial targeting sequence (71). Although the substrate binding pocket of CYP24-SV is apparently functional, the enzyme, trapped in the cytosol, appears to be catalytically inactive. This suggests that, in macrophages, robust 1,25D signaling is maintained over an extended period of time, which would be advantageous for combating intracellular pathogens such as *M. tuberculosis*. It also provides at least part of the molecular basis for the excessive production of 1,25D by macrophages in granulomatous diseases such as sarcoidosis (41).

1,25D IS A DIRECT INDUCER OF ANTIMICROBIAL INNATE IMMUNITY

We have had molecular evidence that 1,25D is a regulator of innate immune responses for several years. It has been known since the early 1990s that expression of the coreceptor of TLR4, CD14, is strongly induced by 1,25D in human cells (63). This regulation is conserved in the mouse; for example, recent work showed that induction of CD14 expression by 25D was abrogated in mice lacking CYP27B1 (79). This study also showed that vitamin D signaling enhanced the expression of TLR2 approximately twofold in human keratinocytes. Given that signaling through either TLR2 or TLR4 enhances vitamin

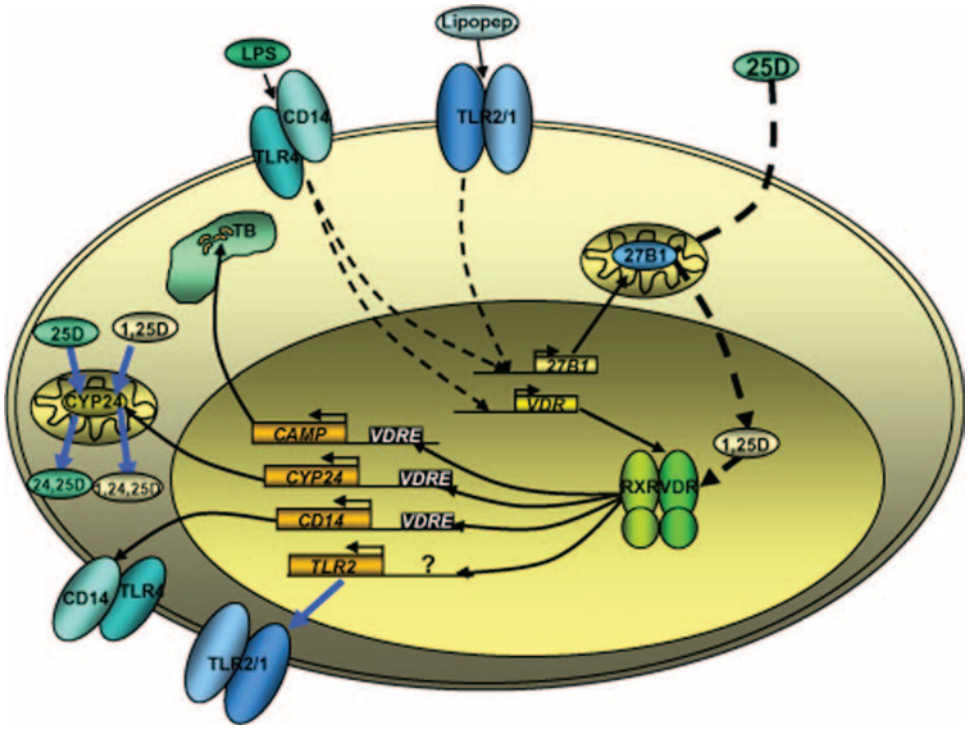

FIG. 1. Schematic representation of the interplay between TLR and vitamin D signaling described in the text. The blue arrows indicate pathways that are active in keratinocytes but not in monocyte/macrophages. Abbreviations: 27B1, CYP27B1; lipopep., triacyl lipopeptides.

D signaling by upregulating expression of the VDR and CYP27B1, the effects of 1,25D on TLR2 and CD14 expression in keratinocytes constitute a positive feedback loop (Fig. 1). Notably, however, recent findings suggest that such a loop does not function in monocytes. Treatment of human monocytes with 1,25D suppressed expression of both TLR2 and TLR4 mRNA and protein in a time- and dose-dependent manner (78). Signaling through TLR2 was suppressed in 1,25D-treated monocytes, as was signaling through TLR4 in the presence of lipopolysaccharide, even though CD14 expression was induced by 1,25D. The authors speculated that downregulation of pattern recognition receptors by 1,25D in antigen-presenting cells may contribute to the capacity of 1,25D to attenuate excessive Th1-driven inflammatory responses and potential downstream autoimmunity (78).

Given that the VDR is a transcription factor and acts as a ligand-regulated gene switch, its signaling is ideally suited to analysis using genomic approaches. Coworkers and I have used a combination of microarrays and in silico screens for VDREs to identify several hundred 1,25D target genes (4, 48, 96, 100). Microarray analysis showed that *CD14* was induced 27-fold by 1,25D in well-differentiated human squamous carcinoma cells, for example (48), and in silico analysis identified an upstream VDRE in the human *CD14* gene (96). In the course of in silico screening for VDREs, we noted that two genes encoding the antimicrobial peptides (AMPs) cathelicidin antimicrobial peptide (CAMP, hCAP18, LL37) and DEFB2 (DEFB4, β-defensin 2) contained promoter-proximal consensus DR3-type response elements (95). Further analysis of the *CAMP* and *DEFB2* VDREs showed that both elements bound VDR/RXR heterodimers in a 1,25D-dependent manner in vitro and in cells in culture and functioned in reporter gene assays (95). *CAMP* expression was strongly stimulated by 1,25D in all cell types examined (epithelial cells, macrophages/monocytes, and neutrophils), whereas *DEFB2* expression was modestly induced in cells of epithelial origin. The strong induction of *CAMP* by 1,25D was subsequently observed by other workers in a range of cell types (32, 50), including in 1,25D-treated or UVB-irradiated human skin biopsies (98), clearly indicating that 1,25D is a primary inducer of the gene. On the other hand, 1,25D is likely to be a secondary regulator of *DEFB2* expression. For example, while 1,25D augmented basal *DEFB2* expression ~2-fold, it enhanced the strong stimulation induced by interleukin-1β to the same degree (95).

AMPs are vanguards of innate immune responses against bacterial, fungal, and viral attack, and many act directly by disrupting the integrity of pathogen membranes (35, 42, 66). In addition, CAMP and some β-defensins can function as chemoattractants for neutrophils, monocytes, and other cellular components of immune responses (51). The induction of AMP expression by 1,25D in humans provides a potential molecular basis for the accumulating evidence, documented above, that a vitamin D-replete state provides broad protection against a range of bacterial and viral pathogens. For example, defensin expression is induced in response to *H. pylori* infection in the gastric mucosa (99) and rhinovirus infection in airway epithelia (68), suggesting that 1,25D-induced DEFB2 expression may provide some protection against these agents. In addition, while there are conflicting results concerning the role of vitamin D signaling in controlling HIV infection, it should be noted that human cathelicidin inhibited the replication of a number of HIV isolates (9) and that the human and porcine

homologues reduced the infectivity of lentiviral vectors (83), suggesting that vitamin D signaling may indeed induce antiretroviral activity.

SPECIES-SPECIFIC MECHANISMS OF AMP EXPRESSION

Although classes of AMPs are conserved, there is considerable interspecies variation in both gene sequence and number and in tissue distribution and regulation of expression. α-, β-, and θ-defensins contain six disulfide bond-forming cysteines (66), and subclasses are distinguished by different spacings of Cys residues. While β-defensins are widespread in vertebrates, α-defensins are mammalian, and θ-defensins are primate specific. The five human α-defensins are expressed in myeloid or enteric tissues, whereas the 19 murine genes (cryptdins) are only enteric. Cathelicidins are cationic and defined for their N-terminal cathelin domain, which is cleaved during maturation. Mice and humans have single cathelicidin genes, whereas there are multiple cathelicidin peptides in bovine species (103).

Apart from variations in gene number and the tissue distribution of expression, there are also differences in gene regulation between species. Notably, neither of the VDREs in the *CAMP* and *DEFB2* genes is conserved in mice, and Gombart et al. (32) noted that the *CAMP* VDRE is imbedded in an *Alu* repeat, which is a human- or primate-specific transposable element. This lack of conservation is noteworthy in light of differences that have emerged in regulation of AMP expression in humans and mice. It was established by 2001 that stimulation of TLR2 on either human or mouse macrophages led to induction of antimicrobial activity against TB infection (13, 88). Induction of antimicrobial activity in murine macrophages is dependent on inducible nitric oxide synthase activity. Remarkably, however, whereas inducible nitric oxide synthase inhibitors blocked induction of AMP activity in mouse macrophages, they had no such effect in human cells.

The mechanism of induction in human macrophages was unclear until the discovery of the TLR2/1-stimulated expression of both *CYP27B1* and *VDR* in human cells, leading to the induction of *CAMP* under conditions of 25D sufficiency (50) (Fig. 1). Moreover, in 25D-treated human cells, CAMP protein was shown to colocalize with mycobacteria in phagolysosomal structures. Subsequently, knockdown of *CAMP* expression in TB-infected human THP-1 macrophage-like cells confirmed that its induction is essential for 1,25D-stimulated antimycobacterial activity (52). Whether vitamin D signaling is induced in murine macrophages remains unclear. However, even if induction of *CYP27B1* and *VDR* does occur, it would be unlikely to lead to CAMP expression because of the lack of a VDRE in the murine CAMP gene.

CAMP expression is also strongly induced in human keratinocytes under epithelial wound healing conditions (18, 25, 36). In *CYP27B*$^{-/-}$ mice, however, under conditions where *CYP27B1* ablation completely eliminated the strong injury-induced expression of CD14, induction of CAMP expression was mildly attenuated, but the effect did not achieve statistical significance (79). It has been argued that regulation of AMP expression in mice and humans has diverged because mice use nitric oxide as an intermediate in innate immune signaling and are nocturnal, whereas humans acquire vitamin D from exposed skin during the daytime (50).

Taken together, the interplay between 1,25D and TLR signaling and the direct induction by 1,25D of AMP gene expression provide a strong molecular basis for epidemiological evidence documenting the protective effects of a vitamin D-replete state against infectious diseases. These factors also underline a growing consensus among researchers (11, 38, 40, 93) that the widespread vitamin D insufficiency/deficiency observed in North American and European populations strongly supports revising upward the recommendations for adequate daily intake of vitamin D (currently 200 IU for children and 400 to 600 IU for adults in these populations) and possibly extending vitamin D supplementation beyond dairy products, as is now practiced in the United States.

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