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The Antibiotic Effects of Vitamin D

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Abstract: The recent discovery that vitamin D regulates expression of the cathelicidin antimicrobial peptide gene has generated renewed interest in using vitamin D to fight infectious diseases. This review describes the historical use of vitamin D or its sources to treat infections, the mechanism of action through which vitamin D mediates its "antibiotic" effects, findings from epidemiological studies associating vitamin D deficiency with increased susceptibility to infection and clinical trials with vitamin D supplementation to treat or prevent infections. Furthermore studies examining an association between vitamin D levels and cathelicidin expression are discussed. The role of cathelcidin throughout the course of infection from the initial encounter of the pathogen to the resolution of tissue damage and inflammation indicates that individuals need to maintain adequate levels of vitamin D for an optimal immune response. In addition, for treating infections, carefully designed randomized, clinical trials that are appropriately powered to detect modest effects, target populations that are severely deficient in vitamin D,and optimized dose, dosing frequency and safety are needed.

Keywords: Antimicrobial peptide, cathelicidin, infection, innate immunity, vitamin D, vitamin D receptor.

"Sol est remediorum maximum"

-Pliny the Elder

HISTORY OF THE ANTIBIOTIC VITAMIN D

When the elder Pliny wrote 'Sun is the best remedy', discovery of vitamin D, the 'sunshine vitamin', was over two thousand years away. Nonetheless, sun light has been utilized to promote human health since the very beginning of medicine. Hippocrates pioneered heliotherapy as he prescribed sunbathing to restore health in Ancient Greece [1]. In the late 1800s and early 1900s, sun exposure gradually became part of the standard treatment for tuberculosis [2, 3]. In 1903, the Nobel Prize in Physiology or Medicine was awarded to Niels Ryberg Finsen, who found that concentrated rays from carbon arc lights were effective in treating lupus vulgaris - a skin infection by *Mycobacterium tuberculosis* [4]. In the 1920s and 1930s, the 'sunshine vitamin' was finally isolated and a mechanistic relationship between sun light and vitamin D was described as exposure of skin to ultraviolet (UV) radiation converted 7-dehydrocholesterol to vitamin D_3 (Fig. **1**) [5].

Another form of vitamin D, termed vitamin D_2, is synthesized by yeast and fungi when ergosterol present in their cell membranes is exposed to UVB radiation [6]. For both 7-dehydrocholesterol and ergosterol, the B-ring of each molecule is cleaved by the UV-B rays and then a spontaneous isomerization event results in vitamin D (Fig. **1**). Both forms of vitamin D are hydroxylated in the liver by the cytochrome P450 enzyme CYP27A1 to 25-hydroxyvitamin D (25(OH)D) in a substrate-dependent reaction and both forms are hydroxylated once more by the vitamin D-1α-hydroxylase CYP27B1 in the kidney to produce the active form 1α,25-dihydroxyvitamin D (1α,25$(OH)_2$D) [6](Fig. **2**). Circulating 25(OH)Dis a reliable indicator of vitamin D status [7].

In the 1940s, physicians successfully treated lupus vulgaris with very high doses of vitamin D_2 [8, 9]; however, lacking a clear mechanism of action, this treatment was quickly replaced by newly developed antibiotics that targeted *M. tuberculosis* [10, 11]. Almost four decades later, published epidemiology studies showed a correlation between vitamin D deficiency and a higher incidence of infections [12-14]. In 1986, Rook and colleagues reported that vitamin D did not directly kill *M. tuberculosis*; instead it enhanced the intracellular killing by human monocytes [15]. Additionally, Rockett *et al.* demonstrated that 1,α 25-dihydroxyvitamin D_3 was capable of increasing production of nitric oxide (NO^-) by activating inducible nitric oxide synthase (iNOS) in human macrophage-like HL-60 cells [16]. Reactive oxygen species (ROS), another important component of innate immunity were also induced by 1,α 25-dihydroxyvitamin D_3 in human monocyte-derived macrophages [17]. Nevertheless, these putative mechanisms were controversial since the role of NO^- and ROS in bacterial killing by human macrophages is still debated [18, 19].

RECENT FINDINGS ELUCIDATE THE ANTIBIOTIC MECHANISM OF VITAMIN D

The underpinning mechanism of vitamin D-induced bacterial killing in macrophages remained enigmatic until three independent groups simultaneously identified that 1,α 25-dihydroxyvitamin D_3 directly activated the human cathelicidin antimicrobial peptide gene (*CAMP*), an important effector peptide in innate immunity, through the

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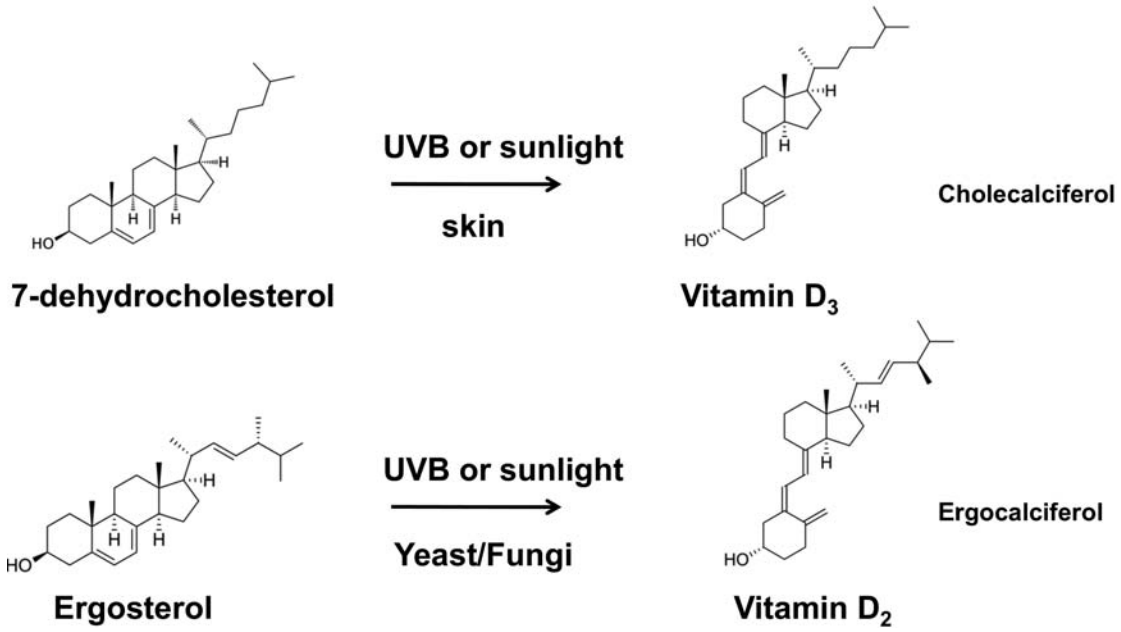

Fig. (1). Synthesis of vitamin D in response to sunlight or ultraviolet (UV) B rays. In skin, natural sunlight or artificial ultraviolet UV B rays cleave the B-ring of 7-dehydrocholesterol to produce cholecalciferol or vitamin D_3. In a very similar reaction in yeast or fungi, ergosterol is cleaved to produce ergocalciferol or vitamin D_2.

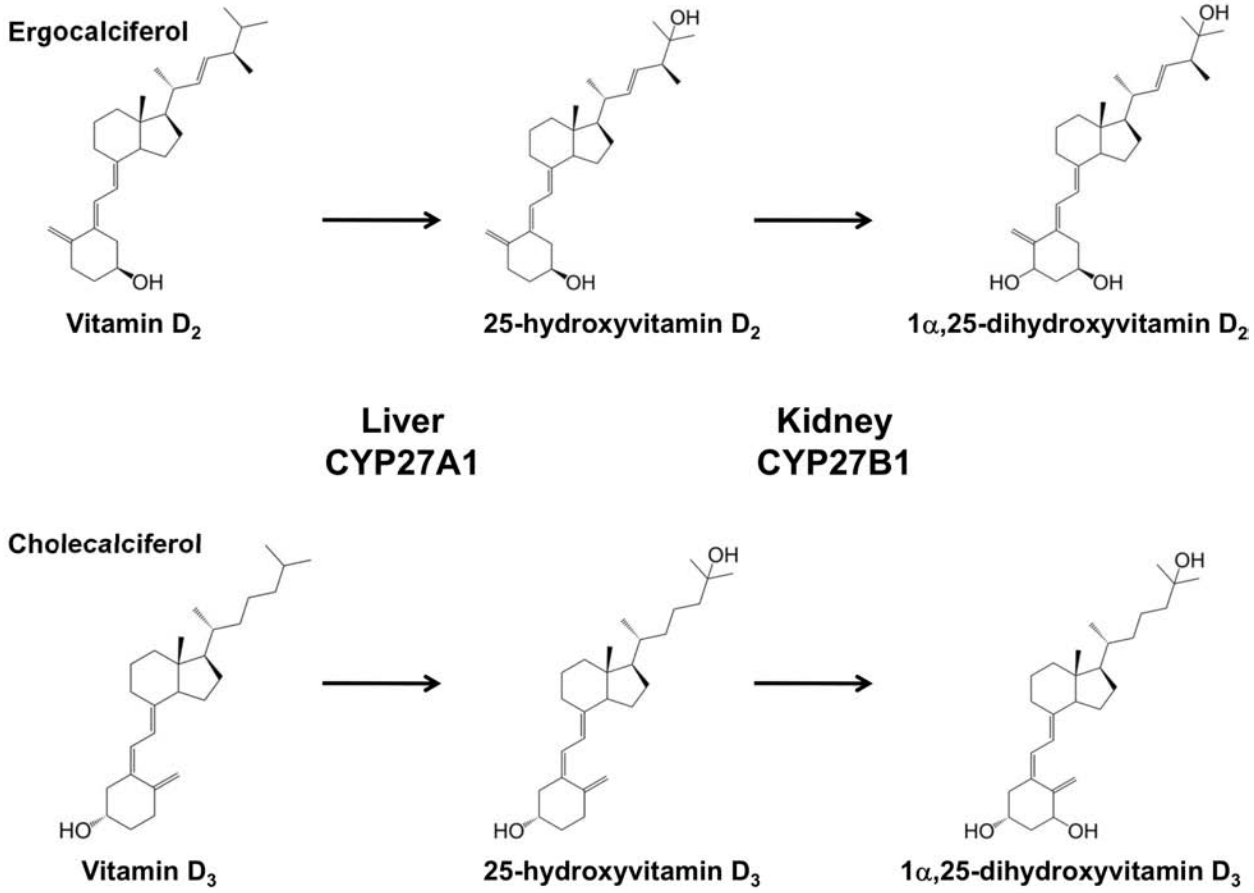

Fig. (2). Vitamin D2 and D3 are converted into active vitamin D. Both vitamin D_2 and D_3 are hydroxylated in the liver by the enzyme CYP27A1 into 25(OH)D. This form circulates in the blood and serves as a reliable indicator of vitamin D status in people. 25(OH)D form is converted by the CYP27B1 enzyme into the bioactive form, $1\alpha,25(OH)_2D$, that binds to the vitamin D receptor and activates gene expression. The kidney is a primary site for this synthesis, but it also occurs in extra-renal cells that express CYP27B1. Immune-activated macrophages produce significant amounts of CYP27B1 and $1\alpha,25(OH)_2D$.

vitamin D receptor (VDR) [20-22]. Based on these findings, Liu *et al.* examined vitamin D-induced *CAMP* expression during *M. tuberculosis* infection and found that the Toll-like receptor 2 (TLR2) agonist 19-kD lipopeptide derived from *M. tuberculosis* induced *CAMP* expression in human monocytes only in the presence of adequate levels of $25(OH)D_3$ [23]. This increase in *CAMP* gene expression, in turn, enhanced intracellular *M. tuberculosis* killing by monocytes [23]. The same group later demonstrated that *M. tuberculosis* killing by vitamin D was mainly mediated by CAMP [24]. Furthermore, CAMP-dependent autophagy also participated in intracellular killing of *M. tuberculosis* by vitamin D [25, 26]. It was shown that $1,25(OH)_2D_3$ induced expression of the autophagy-related genes *Beclin-1* and *Atg* and increased the colocalization of mycobacterial phagosomes with autophagosomes in human macrophages in a cathelicidin-dependent fashion. In addition, the anti-mycobacterial activity in human macrophages mediated by physiological levels of $1,25(OH)_2D_3$ required autophagy and CAMP. In addition, interferon-γ (INF-γ), the pivotal cytokine produced by T cells in response to *M. tuberculosis*, required vitamin D induced CAMP to enhance macrophage killing [27, 28]. Recently vitamin D was demonstrated to down-regulate the hepcidin antimicrobial peptide (HAMP) gene [29]. This would decrease ferroportin protein which could decrease intracellular iron levels. High intracellular iron levels are beneficial for *M. tuberculosis* growth; therefore, this down-regulation would help combat infection. The discovery that vitamin D regulates antimicrobial gene expression has spurred many recent epidemiology studies that have shown a correlation between vitamin D deficiency and increased risk or severity of tuberculosis, supporting similar findings made in the 1980s [30-39].

These new findings stimulated a renewed interest in using vitamin D to improve treatment outcomes in pulmonary tuberculosis patients, even though its effectiveness in clinical studies was ambiguous. Martineau *et al.*, reviewed three randomized controlled trials and 10 case series and concluded that the prior studies were flawed methodologically [40]; nevertheless, two small randomized studies suggested beneficial effects of vitamin D on treatment of TB [41, 42]. Also, when patients were given a single oral dose of 2.5 mg vitamin D the ability of their whole blood to restrict BCG growth *in vitro* was greatly enhanced without affecting antigen-stimulated IFN-γ responses [40]. On the other hand, in a larger double-blind, randomized, placebo-controlled trial vitamin D did not improve clinical outcome or mortality among TB patients [43]. The authors concluded that the dose used was insufficient as both the placebo and treated groups had similar levels of vitamin D at the start of the trial and at two and eight months after treatment [43]. More recently, Martineau *et al.* reported that a 100,000 IU/week vitamin D supplement with standard pulmonary tuberculosis treatment significantly accelerated sputum culture conversion in patients with the *tt* genotype of the vitamin D receptor when compared to patients with placebo and standard treatment [44]. With the same treatment protocol and more rigorous data analysis methods, the same group conducted another clinical trial and concluded that vitamin D supplementation accelerated sputum smear conversion as well as other clinical outcomes in pulmonary tuberculosis [45]. In a randomized double-blinded, multicenter, placebo-controlled clinical trial, 259 patients were given 600,000 IU vitamin D3 two times (once per month for two months) intramuscularly. The vitamin D-treated patients showed a significantly greater average weight gain and lower residual disease by chest x-ray [46].

In addition to TB, low serum levels of vitamin D are associated with bacterial vaginosis in the first trimester of pregnancy [47] and negatively impact the progression of disease in HIV-infected individuals [48, 49]. A higher incidence of influenza A infections was observed in deficient individuals [50] and a randomized, double-blind, placebo-controlled study showed that a 1,200 IU/day supplement of vitamin D lowered the incidence of seasonal flu in school children [51]. Similarly, vitamin D was found protective against flu in both elderly people and African American women [52-54]. Also, vitamin D deficiencies were associated with an increased incidence of respiratory tract infections [55] and a clinical trial showed that 4,000 IU/day of vitamin D lowered the severity of upper respiratory tract infections [56]. On the other hand, no obvious difference in the incidence and duration of severity of upper respiratory tract infections (URIs) between vitamin D (2000 IU/day) and placebo groups was observed after 12 weeks [57] and another study found that vitamin D status was not a risk factor in hospitalization for ALRI [58]. In summary, the role of vitamin D in infectious diseases has been increasingly recognized, but is clear that further controlled, randomized, clinical trials need to be appropriately powered to detect modest effects and investigators need to optimize the dose, dosing frequency and target populations that are severely deficient in vitamin D.

THE HUMAN CATHELICIDIN ANTIMICROBIAL PEPTIDE (CAMP) GENE

Regulation of *CAMP* gene expression by vitamin D is thought to mediate many of its antibiotic effects. The role of the CAMP gene in immune function and its regulation by vitamin D is reviewed in the following sections.

In 1991, the first mammalian cathelicidin was identified in rabbit bone marrow as an 18kD lipopolysaccharide (LPS)-neutralizing protein and named CAP18 [59]. Later, the same group reported that the C-terminal 37 amino acids of CAP18 not only bound to LPS but also directly killed both gram-positive and gram-negative bacteria [60, 61]. In 1995, two independent groups cloned the human cathelicidin gene from granulocytes [62, 63]. The newly identified protein was named hCAP18. Like its counterpart in rabbit, the C-terminal 37 amino acids of hCAP18 (later named LL-37) also conferred its bactericidal activity [64]. Several cathelicidins were also identified in other mammals and Zanetti *et al.* recognized the structural similarity of these proteins and named the family of proteins cathelicidin [65]. Cathelicidins have an N-terminal signal sequence targeting the endoplasmic reticulum (ER) and a highly conserved cathelin domain followed by a positively charged C-terminal antimicrobial domain (Fig. **3**).

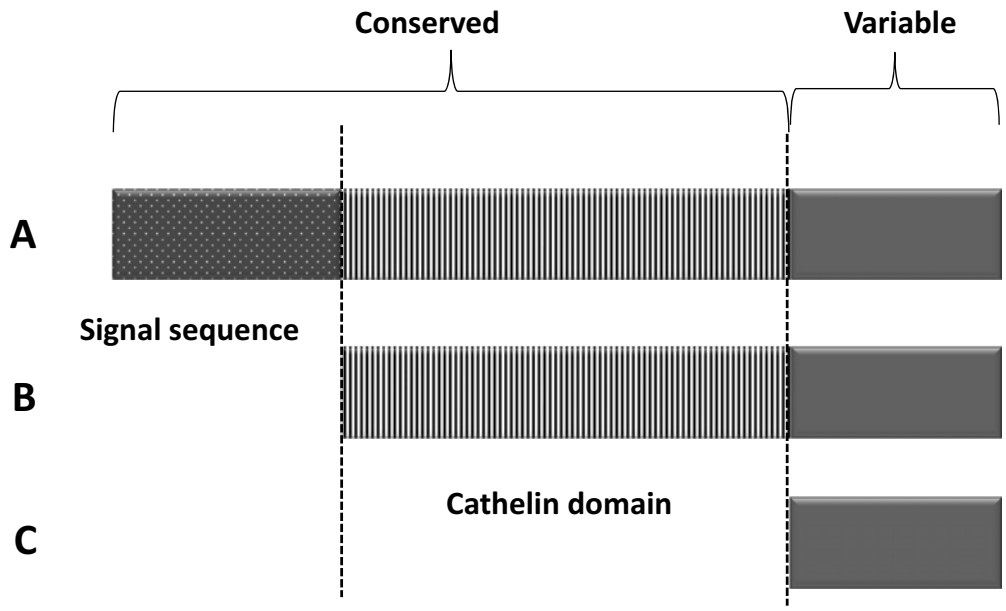

Fig. (3). Domain structure of the cathelicidin family. A) The cathelicidin pro-peptide is composed of three domains: 1) the N-terminal signal sequence, 2) the cathelin domain and 3) the C-terminal antimicrobial peptide domain. **B**) The cathelicidin pro-peptide is stored in specific granules of neutrophils and is referred to as hCAP18. **C**) The active C-terminal peptide is referred to as LL-37 in humans.

LL-37 is an Antimicrobial Peptide

Bactericidal Function of LL-37

Larrick *et al*. reported that LL-37 was capable of killing both gram-positive and gram-negative bacteria, including *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhimurium* [64]. Over the years, LL-37 has demonstrated broad spectrum antimicrobial capacity against bacteria. Notably, LL-37 killed several antibiotic resistant bacterial strains such as methicillin-resistant *S. aureus* (MRSA), suggesting that activating the human CAMP gene may be an effective way to combat drug-resistant bacterial infections [66, 67]. As with most antimicrobial peptides, LL-37 kills bacteria by disrupting the cell membrane [66, 68].

Anti-Biofilm Effect of LL-37

Many bacterial species that cause persistent infections form biofilms. Recently, LL-37 was found to inhibit *P. aeruginosa* biofilm formation, which is the critical factor leading to chronic infections in cystic fibrosis patients [69, 70]. LL-37 suppresses biofilm formation in other microbes including *Francisella novisida* [71], uropathogenic *E. coli* [72], *S. aureus*[73], *Aggregatibacter actinomycetemcomitans* [74], *Stenotrophomonas maltophilia* [75] and *Burkholderia pseudomallei* [76]. Several factors contribute to LL-37's role in inhibiting *P. aeruginosa* biofilms. Overhage *et al*. showed that LL-37 suppressed the quorum-sensing systems in *P. aeruginosa* by down-regulating *lasI* and *rhlR*. In addition, LL-37 also inhibited genes required for assembling of flagella - a crucial component in initiating adherence during biofilm formation [69]. Dean *et al*. showed that LL-37 also altered the expression of *rhl*A and *rhl*B, two other genes implicated in biofilm formation by *P. aeruginosa* [73]. Nevertheless, the mechanism by which LL-37 blocks biofilm formation by other bacteria remains largely unknown. Interestingly, LL-37 usually inhibits biofilms at sub-microbicidal concentrations. For example, LL-37 prevented *P. aeruginosa* biofilm formation at 0.5 μg/ml, whereas the minimum inhibitory concentration for *P. aeruginosa*is 64 μg/ml [69]. Similar findings were reported for inhibition of other biofilms (*A. actinomycetemcomitans* [74], uropathogenic *E. coli* [72]), suggesting that biofilm inhibition might be a more physiologically relevant function of LL-37 rather than direct bacterial killing which usually requires higher concentrations of the peptide.

Other Antimicrobial Functions of LL-37

LL-37 inhibits the growth of viruses. In 2004, Howell *et al*. published the first report showing that LL-37 directly kills vaccinia virus [77]. The list of viruses susceptible to LL-37 killing has expanded over the years. To date, LL-37 is known to inhibit growth of herpes simplex virus type 1 (HSV-1), adenovirus (Ad19), human immunodeficiency virus 1 (HIV-1), influenza A virus (IAV) and varicella zoster virus (VZV) [78-83]. In addition to viruses, LL-37 also kills fungi and parasites. *Candida albicans* was inhibited by LL-37 through membrane disruption [66, 84]. Rico-Mata *et al.* discovered that LL-37disrupted the membrane integrity of *Entamoebahistolytica* trophozoites [85].

LL-37 Modulates Innate and Adaptive Immune Reponses

LL-37 exhibits a wide range of immune modulatory functions [86]. As an alarmin, LL-37 signals danger and chemoattracts immune cells including monocytes, neutrophils, T cells and mast cells and regulates cytokine production in these cells [87]. LL-37 also regulates apoptosis and promotes angiogenesis and wound healing [88]. LL-37 exerts these functions through an array of transmembrane receptors as highlighted in the following sections.

Formyl Peptide Receptor 2 (FPR2)

FPR2 is a pertussis toxin (PTX) sensitive Gi protein-coupled transmembrane receptor [89]. Upon LL-37 binding, FPR2 mobilizes Ca^{2+} and initiates chemotaxis [90]. It is widely expressed in neutrophils, monocytes and T cells [91, 92]. LL-37 recruitment of neutrophils and monocytes is important in clearing invading microbes or dead host cells. Mice lacking cathelicidin exhibit a delayed neutrophil infiltration in lung and as a result experience more severe infections [93]. Along with chemotaxis, activation of FPR2 in neutrophils inhibits apoptosis, enabling these cells to produce more cytokines [94]. FPR2 is also expressed by endothelial cells and activation by LL-37 promotes proliferation of endothelial progenitor cells and enhanced angiogenesis [95]. Interestingly, activation of FPR2 by LL-37 enhances epithelial cells lifespan by suppressing apoptosis and secondly, FPR2 signaling feeds into pathways that up-regulate cell migration and proliferation, both of which are crucial to wound healing [96, 97].

Toll-Like Receptors (TLRs)

LL-37 interacts with TLR ligands and modulates TLR signaling. As noted previously, LL-37 binds TLR4 ligand LPS and neutralizes its down-stream signaling in macrophages including the release of tumor necrosis factor alpha (TNFα) and NO^- production [66, 98-100]. Blocking of TLR signaling by LL-37 protects mice and rats from gram-negative bacterial sepsis [101, 102]. LL-37 also forms complexes with negatively charged DNA or RNA molecules, which are recognized by TLR7, TLR8, TLR9 or TLR3. In psoriatic skin, LL-37 binds to self-DNA molecules released from damaged cells, delivers the otherwise extracellular molecules across the membrane and presents them to the intracellular TLR7/8 receptors. The activation of TLR7/8 enhanced type I interferon production in plasmacytoid dendritic cells contributes to the pathogenesis of psoriasis [103, 104]. *Via* the same mechanism, LL-37 augments TLR9 induced type I interferon production in keratinocytes [105]. LL-37 complexes with the TLR3 agonist polyinosine-polycytidylic acid (poly(I:C)); however, LL-37's effect on TLR3 signaling seems to be cell-type specific. In human fibroblasts, LL-37 was reported to suppress poly(I:C) induced interleukin 6 (IL6), interleukin 8 (IL8), and C-X-C motif chemokine 10 (CXCL10) expression [106], but IL6 and IL8 production was up-regulated in human bronchial epithelial cells by the combination of poly(I:C) and LL-37 [107, 108]. On the other hand, Hasan *et al.* showed LL-37 blocked poly(I:C) mediated TLR3 signaling in mouse macrophages, dampening type I interferon production in these cells.

P2X7

Purinergic receptor P2X7 participates in transmembrane signaling of LL-37, although its legitimacy as a LL-37 receptor remains controversial [109]. LL-37 induced IL1 release from human monocytes depends on P2X7 [110]. In addition, LL-37 activation of P2X7 increases cell migration in intestinal epithelial cells [111] and stiffness in endothelial cells [112] as well as IL8, cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) production in gingival fibroblasts [113, 114].

Other Transmembrane Receptors

Several alternative LL-37 receptors have also been identified. LL-37 stimulates monocyte migration through chemokine (C-X-C motif) receptor 2 (CXCR2) [115]. Mas-related gene X2 (MrgX2) mediated LL-37 induced chemotaxsis and degranulation in mast cells [116]. LL-37 transactivates epidermal growth factor receptor (EGFR) in airway epithelial cells and keratinocytes, stimulating cell migration and proliferation [117-120]. Interestingly, activation of EGFR appears to be independent of the structure of LL-37 since the peptide made of enantiomers also activated EGFR [121].

These additional biological activities of LL-37 raise an interesting question: does the vitamin D-CAMP pathway mediate additional health outcomes beyond immune response in which vitamin D has been implicated? To address this question it is important to understand what impact vitamin D has on *in vivo* expression of the CAMP gene.

THE EFFECT OF VITAMIN D ON HUMAN CATHELICIDIN EXPRESSION

Human CAMP is widely expressed by the cells comprising the first line of defense against invading microbes. Neutrophils are the predominant source of hCAP18 (about 0.6 μg/10^6 cells), where it is packaged in specific granules [63]. Secretion from bone marrow is believed to be the major contributor of hCAP18 in blood (about 1.2 μg/ml), which is higher than many other specific granule proteins in the serum [122]. To a lesser extent, other immune cells including macrophages [22], dendritic cells [123], mast cells [124], monocyte, natural killer cells, γδ T cells and B cells [125] all produce CAMP. A hierarchy of expression exists in peripheral blood cells with neutrophils expressing the most hCAP18, monocytes the next most and lymphocytes the least [126]. In skin, keratinocytes produce hCAP18 and store it in lamellar bodies [127]. Additionally, CAMP is expressed by epithelial cells in the intestinal [128], respiratory [129] and urogenital tracts [130].

CAMP expression is regulated by cytokines, bacterial components and environmental stimuli [131]. For example, skin injury causes keratinocytes to release CAMP [132, 133]. Psychological stress, on the other hand, decreases CAMP expression in skin [134]. The centerpiece of transcriptional regulation of CAMP expression is the vitamin D signaling pathway [20-22]. As shown in Fig. **4**, $1\alpha,25(OH)_2D$, the active hormone of vitamin D, up-regulates *CAMP* expression through a VDR/RXR heterodimer binding to the *CAMP* promoter. Much of the regulation of *CAMP* expression is through the modulation of the vitamin D signaling pathway (Fig. **5**). A key regulatory point is expression of the *CYP27B1* gene which produces $1\alpha,25(OH)_2D$. TLR2 ligand 19-kD *M. tuberculosis* derived lipopeptide increases the expression of CYP27B1 and thus *in situ* production of $1\alpha,25(OH)_2D$ in an IL15 dependent manner [23, 135]. Induction of CYP27B1 and augmentation of vitamin D-induced CAMP expression was also found in TLR8 agonist treated human macrophages [136] and in response of lung cells to RSV infection *via* TLR3 [137]. Transforming growth factor beta 1 (TGF-β1), a growth factor that keratinocytes release in response to skin injury, induce CYP27B1 levels and thus increased CAMP

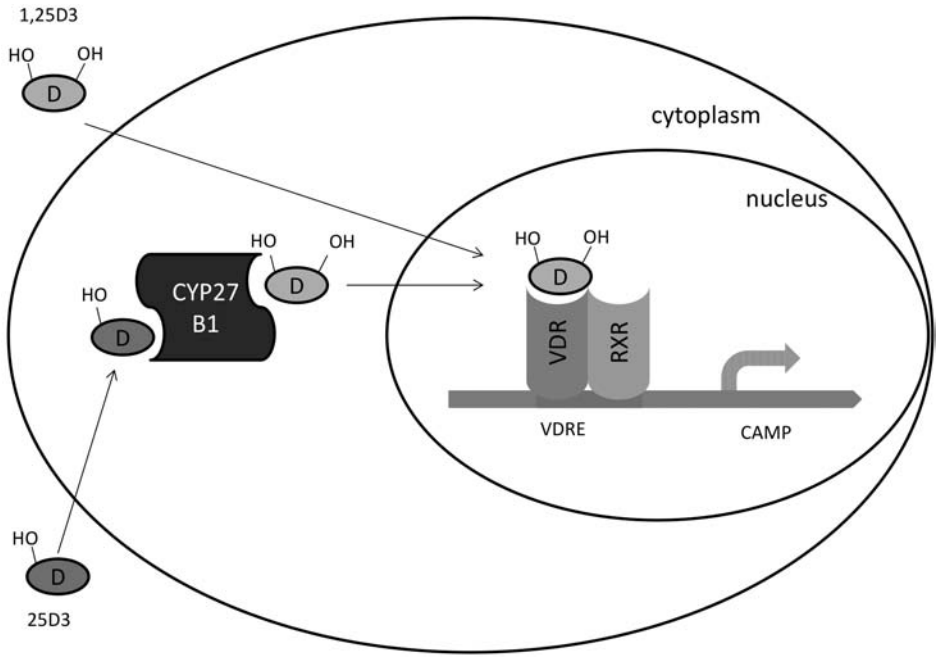

Fig. (4). CAMP is a VDR target gene. Upon ligand binding, VDR dimerizes with RXR and migrates into nucleus, where the VDR/RXR dimer binds to a vitamin D response element (VDRE) and initiates *CAMP*gene expression. The ligand for VDR is 1α,25(OH)$_2$D, which is produced by hydroxylation of 25(OH)D. This reaction is performed by CYP27B1 and can occur in either the kidney or locally in immune activated macrophages.

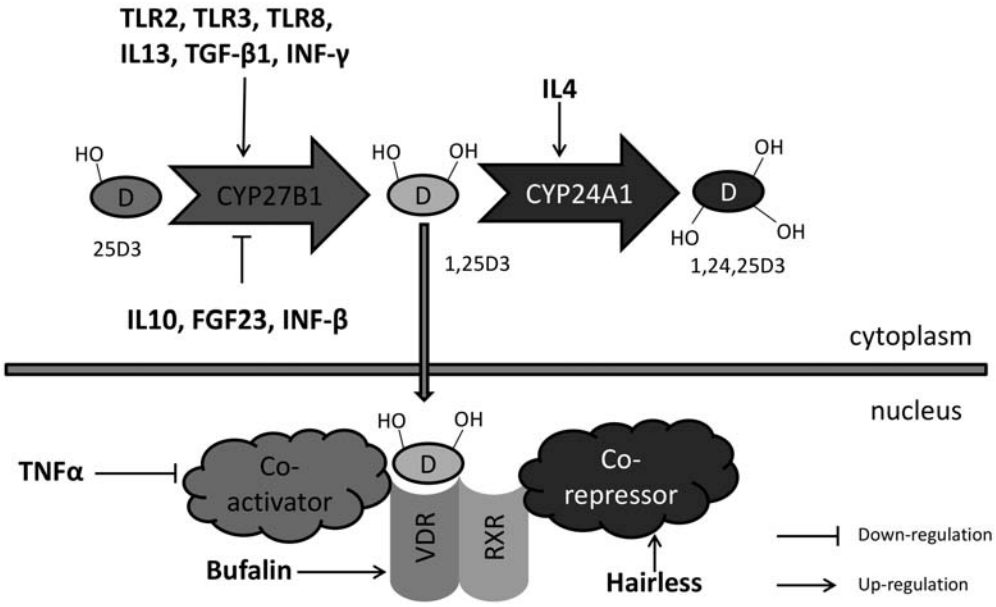

Fig. (5). Regulation of the CAMP gene through modulation of the vitamin D pathway. CYP27B1 is the rate-limiting enzyme controlling *in situ* production of active 1α,25(OH)$_2$D. CYP24A1 hydroxylates both 25(OH)D and 1α,25(OH)$_2$D and initiates its catabolism. These two cytochrome P450 enzymes control the availability of 1α,25(OH)$_2$D locally. Expression of these enzymes is targeted by various growth factors and cytokines as described in the text. Expression of the VDR/RXR transcription factor and its associated coregulators are targeted by proteins and other factors that can modulate expression of vitamin D target genes as described in the text.

expression in keratinocytes [138]. The T cell cytokine interferon-γ also activates vitamin D-induced CAMP expression by up-regulating CYP27B1 in macrophages [139], as did IL13 in bronchial epithelial cells [140]. In contrast, fibroblast growth factor 23 (FGF23), IL10 and interferon-β (IFNβ) suppress CYP27B1 in human monocytes. This suppresses vitamin D induced CAMP expression [28, 141].

Two other points for modulation of the vitamin D pathway are regulation of expression of the vitamin D-24-hydroxylase (CYP24A1) an enzyme that initiates catabolism of 1α,25(OH)$_2$D and 25(OH)D and expression of the VDR. For example, the T cell cytokine IL4 lowered 1α,25(OH)$_2$D$_3$ concentration by up-regulating CYP24A1 activity in macrophages, thereby suppressing CAMP gene expression

[139] and bufalin, a compound isolated from traditional Chinese medicine, augmented 1α,25$(OH)_2$D induced CAMP by increasing VDR expression (Fig. **5**) [142].

In addition to increasing VDR levels regulating expression of coactivators/corepressors that interact with the VDR can modulate vitamin D-induced *CAMP* gene expression. In keratinocytes, hairless (HR), a coregulator of VDR, suppressed vitamin D induced *CAMP* expression by enhancing VDR binding to the nuclear receptor corepressor (NRC). This formed a repressive complex and subsequently decreased *CAMP* expression [143]. Similarly, TNFα inhibited expression of the VDR coactivator steroid receptor coactivator-3 (SRC-3) in human alveolar macrophages and suppressed vitamin D-induced *CAMP* expression (Fig. **5**) [144].

The regulation of CAMP gene expression is conserved only in humans and primates; therefore, an animal model to study this pathway does not exist [22, 145]. Thus, elucidating the importance of this biological pathway requires carefully designed studies in humans and primates.

VITAMIN D STATUS AND CATHELICIDIN LEVELS

Because 1α,25$(OH)_2$D increases *CAMP* gene expression, regulating *in vivo* hCAP18 levels may be possible with vitamin D. In an early study, only a modest positive correlation between hCAP18 and 1α,25$(OH)_2$D levels, but not 25(OH)D levels was observed in kidney dialysis patients measured at the beginning of their treatment; however, high levels of hCAP18 were associated with a significant decrease in 1-year mortality [146]. For sepsis patients, decreased levels of 25(OH)D, vitamin D binding protein (DBP) and hCAP18 were associated with more severe illness and a positive association between 25(OH)D and cathelicidin levels was observed in all patients [147]. In healthy individuals, a positive association between circulating 25(OH)D and hCAP18 levels was observed when 25(OH)D levels were below 32 ng/ml, but not above [148, 149]. An additional study that did not apply a cut-off described a positive correlation [150]. In atopic dermatitis patients a positive correlation of serum 25$(OH)D_3$ with cathelicidin levels was observed [151]. In contrast, no association was observed in cord-blood samples or in patients with active TB [37, 152]. Also, in patients with community acquired pneumonia a correlation was not observed [153]. The current studies suggest that serum levels of vitamin D may be associated with hCAP18 levels, but the mixed findings indicate that additional research with both healthy individuals and those suffering from various disease conditions is needed.

Several studies suggest that supplementation with vitamin D may increase CAMP expression. Atopic dermatitis patients supplemented with 4,000 IU/day of oral vitamin D for 21 days showed increased cathelicidin expression in skin lesions and a mild increase in unaffected skin, but a decrease in skin infection was not determined [154]; however, in a second study with more patients this was not observed [155]. A study of deficient patients visiting a bone clinic did not show an increase in hCAP18 levels after supplementation for five weeks with 50,000IU twice weekly [156]. High dose supplementation (50,000 IU/week for 12 weeks) of patients with early chronic kidney disease did not increase cathelicidin serum levels [157]. In vitamin D deficient healthy women receiving 60,000 IU vitamin D_3 per week, cathelicidin levels did not increase [158]. Interestingly, narrowband UV-B treatment of atopic dermatitis and psoriasis patents improved serum 25$(OH)D_3$ levels and increased cathelicidin levels in the skin or serum [159, 160]. In contrast to these findings, the same treatment did not increase the levels of cathelicidin in the skin of hemodialysis patients [161]. One explanation for the conflicting reports may be that for cathelicidin levels to increase, it is necessary for cells to be activated by TLR signaling or inflammation. For example, *ex vivo* infection of urinary bladder biopsies from post-menopausal women after vitamin D supplementation resulted in an increased induction of the *CAMP* gene and protein expression when compared to biopsies taken prior to supplementation [162]. According to the current model, the induction of cathelicidin is mediated by 1α,25$(OH)_2$D which is synthesized by cells after immune activation and induction of CYP27B1 activity [23]. Investigators need to design future studies to test this possibility. Also, it is important to determine if therapeutic use of the bioactive forms of vitamin D will boost levels of cathelicidin and thus increase protection against infection and/or sepsis.

CONCLUSIONS

In vitro studies of the past 30 years have identified numerous mechanisms for the antibiotic effects of vitamin D in humans with induction of antimicrobial or bactericidal peptides being of greatest interest. In addition, historically, sources of vitamin D have shown efficacy in treating infectious diseases primarily pulmonary and cutaneous (lupus vulgaris) mycobacterium tuberculosis infections. The improvement of lupus vulgaris patients with very high dose vitamin D therapy was quite striking. More recent studies with pulmonary tuberculosis use much lower doses of vitamin D in combination with current antibiotic therapies and the findings are mixed. Studies with other infectious conditions suggest that adequate vitamin D levels or supplementation with vitamin D may be important in reducing respiratory tract and vaginal infections. Again, other studies have shown no benefit, thus researchers need to carefully design future studies that are well-controlled, randomized, clinical trials that are appropriately powered to detect modest effects. Also, investigators need to target populations that are severely deficient in vitamin D, optimize the dose, dosing frequency and safety. While direct killing of pathogens by cathelicidin may explain, in part, the antibiotic properties of vitamin D, the activation of various transmembrane receptors, dampening of TLR signaling and induction of autophagy mediated by this peptide need to be explored more fully to understand how vitamin D functions in modulating the immune response. Because the cathelicidin peptide combats infection at all stages from the initial response of killing microbes and inhibiting biofilms to resolution through recruitment of other immune cells and healing by promoting angiogenesis and migration of epithelial cells in wound healing, it is important for individuals to maintain adequate levels of vitamin D for an optimal immune response.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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