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The role of vitamin D_3 and vitamin B9 (Folic acid) in immune system

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ABSTRACT

Background and aims: Vitamins are essential constituents of our diet that Longley have been known to influence the immune system. Vitamin D_3 and B9 have received particular attention in recent years as these vitamins have been shown to have an unexpected and crucial effect on the immune response. 1, $25(OH)_2D_3$ metabolizing enzymes and vitamin D receptor (VDR) are present in many cell types including various immune cells such as antigen-presenting-cells, T cells, B cells.

Methods: In this mini review, we study 30 novel articles since 2009 to 2015 about the essential roles of vitamins in modulating a broad range of immune processes, such as lymphocyte activation, T-helper-cell differentiation and regulation of the immune response.

Results: 1, $25(OH)_2D_3$ has direct effect on CD^{4+} T (T-helper) cells for suppressing various cytokines such as IFN-γ, IL-17, IL-21 and IL-22, while enhancing the regulatory Tcells. In vitro studies show that Treg cells could be differentiated from naive T cells in vitamin B9-reduced condition.

Conclusions: These findings provide a new link between diet and the immune system, which could maintain the immunological homeostasis and clarify the beneficial roles of vitamins in informing the design of vitamin analogs as pharmacologic agents for the generation and maintenance of a healthy immune condition.

Review article

Keywords: Vitamin D_3, Vitamin B_9, Immune system, Regulatory T Cell.

INTRODUCTION

Vitamins are organic compounds that the host organism cannot synthesize in sufficient quantities and that therefore need to be supplied exogenously by the diet or commensal bacteria. Some vitamins (e.g. vitamin B family and vitamin C) are water-soluble, whereas others (e.g., vitamins A, D, E, and K) are hydrophobic. Both

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hydrophilic and hydrophobic vitamins and their metabolites have diverse functions in many biologic events, including immunologic regulation responses is better. than regulation. Indeed, vitamin deficiency results in high susceptibility to infection and immune diseases.[1] Until the mid-1930s, when the first commercial yeast-extract vitamin B complex and semi-synthetic vitamin C supplement tablets were sold, vitamins were obtained solely through food intake, and changes in diet (which, for example, could occur during a particular growing season) usually greatly altered the types and amounts of vitamins ingested. However, vitamins have been produced as commodity chemicals and made widely available as inexpensive semisynthetic and synthetic-source multivitamin dietary and food supplements and additives, since the middle of the 20th century. Thirteen vitamins are universally recognized at present. Vitamins are classified by their biological and chemical activity, not their structure. The largest number of vitamins, the B complex vitamins, function as precursors for enzyme cofactors, that help enzymes in their work as catalysts in metabolism.[2] In this role, vitamins may be tightly bound to enzymes as part of prosthetic groups: For example, biotin is part of enzymes involved in making fatty acids. They may also be less tightly bound to enzyme catalysts as coenzymes, detachable molecules that function to carry chemical groups or electrons between molecules. For example, folic acid may carry methyl, formyl, and methylene groups in the cell. Although these roles in assisting enzyme-substrate reactions are vitamins' best-known function, the other vitamin functions are equally important. Previously vitamins were thought to regulate the immune system in an indiscriminant manner, but accumulating evidence has revealed specific functions of individual vitamins and their metabolites in immune responses.[3]

Vitamin D is a group of fat soluble vitamins responsible for absorption of calcium and phosphate in the small intestine and stimulates osteoclast differentiation.[4] Two major forms of vitamin D exist. Vitamin D2 (ergocalciferol), found in plants, is produced by ultraviolet B irradiation of ergosterol and can be consumed as a supplement or in fortified foods.[5] Vitamin D_3 (cholecalciferol) is synthesized in the human epidermis or consumed in the form of natural (for example, fish) or fortified food sources or as a supplement.[4] Despite its name, vitamin D is not really a vitamin, it is the precursor to the potent steroid hormone calcitriol (also known as 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), which mediates numerous actions in many tissues of the body.[6] Cutaneous vitamin D_3 generated by high energy UVB photons provides 90% of the human vitamin requirement. The biological half-life of 25-OHD_3 is 2 months, so this metabolite effectively integrates sunlight's energy signal over time.[7] With the finding of the vitamin D receptor (VDR) in nearly every tissue and the more recent discovery of thousands of VDR binding sites throughout the genome controlling hundreds of genes, the interest in vitamin D and its impact on multiple biologic processes has accelerated tremendously as evidenced by the thousands of publications each year for the past several years.[5]

In the human skin, cholecalciferol is synthesized from 7-dihydrocholesterol when exposed to UVB. The production of vitamin D_3 (D_3) in the skin is not an enzymatic process. Vitamin D_3 (cholecalciferol) is produced through a two-step process in which the B ring is broken by UV light (spectrum 280-320 UVB) radiation from the sun, forming pre-D_3 that isomerizes to D_3 in a thermosensitive but noncatalytic process.[8]

Cholecalciferol is biologically inactive and immediately binds to vitamin D binding proteins or albumin.[9] It then enters the circulation and is hydroxylated in the liver, catalyzed by the enzymes CYP2R1 and CYP27A1, which results in the production of the inactive form 25 hydroxy vitamin D (25 (OH)D) which represents the main circulating vitamin D metabolite and is the most reliable parameter to define human vitamin D status.[10] In the kidney, 25 (OH)D is further converted to the circulating biologically active compound calcitriol (1, 25$(OH)_2$D) by the enzyme 1-α-hydroxylase (CYP27B1) which is under strict control of parathyroid hormone and the phosphaturic hormone fibroblast growth factor 23 (FGF-23).[11] Calcitriol levels are tightly regulated in a renal negative feedback loop, including inhibition of CYP27B1 by high levels of calcitriol and FGF-23 and stimulation of the enzyme CYP24A1 (24-hydroxylase) which metabolizes calcitriol into the inactive, water soluble form, calcitroic acid, which is then excreted in the bile.[12] Circulating levels of calcitriol are mainly determined by renal CYP27B1 activity.[13] However, other cell types including immune cells, also express CYP27B1 and are able to convert the inactive, circulating form 25(OH)D into the active hormone in an autocrine or paracrine manner. Especially in immune cells, such as macrophages and dendritic cells, a lack of feedback mechanisms compared to kidney cells allows the production of high local concentrations of calcitriol needed for immune modulation.[14]

Vitamin D receptor (VDR) is a transcription factor and member of the steroid hormone and nuclear hormone receptor family. The VDR was identified in 1969 and its crystal structure was cloned in 1987 and binding to its natural ligand were characterized in 2000.[15] Since its discovery, researchers have detected the VDR in many tissues of the body, including bone, pancreatic β cells, parathyroid gland, brain, skin, prostate, testes, heart, skeletal muscle tissue, breast, liver, lung, intestine, kidneys, adipose cells and immune response cells, such as macrophages, dendritic cells and activated B- and T-cells.[16] It is comprised of 3 domains: the N-terminal DNA binding domain with two zinc fingers that bind to the grooves of the DNA at discrete sites (VDREs), the C-terminal ligand binding domain, and the hinge region binding of these two domains together. The ligand binding domain structure has been solved by x-ray crystallography.[17] It is comprised of 12 helices. The terminal helix serves as a gating mechanism closing around the incorporated ligand and forming an interface for coactivators as well as facilitating the interaction of VDR with its heterodimer partner, generally RXR. Although VDR preferentially binds to RXR, creating a VDR-RXR dimer, VDR can also bind other receptors of the nuclear receptor superfamily, which include thyroid, vitamin A, PPAR-γ and other orphan receptors.[18] The VDR-RXR dimer can regulate genes in several systems and tissues. Although there is substantial variability in quence of VDREs, the most prevalent motif for the VDRE sequence consists of two half-sites, each with the six-nucleotide consensus sequence, GGTCCA, separated by 3 other nucleotides of any sequence. This motif is known as Direct Repeat 3 (DR3), although other configurations of VDRE-binding sites, including DR6 and DR4, exist in some vitamin D-regulated genes.[19] VDR binding to its VDRE then recruits coregulatory complexes required for its genomic activity. These complexes can be both gene and cell specific, enabling the selectivity of 1,25$(OH)_2$D action from cell type to cell type. These complexes include a subunit that directly binds to the VDR generally through an LXXLL motif along with a number of

subunits that contain enzyme activity such as histoneacetyl transferases (coactivators such as the SRC family) ordeacetylases (corepressors such as SMRT and NCoR), methyl transferases and demethylases, ATPase-containing nucleosomal-remodeling activity (SWI/SNF), and links to RNA polymerase II.[5]

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

For many years, the key action of vitamin D on macrophages was thought to be its ability to stimulate differentiation of precursor monocytes to more mature phagocytic macrophages.[20,21] This concept was supported by observations showing differential expression of VDR and 1α-hydroxylase during the differentiation of human monocytes macrophages.[22] The latter report also emphasized early studies showing that normal human macrophages were able to synthesize $1,25(OH)_2D_3$ when stimulated with interferon gamma (IFN-γ). Localized activation of vitamin D, coupled with expression of endogenous VDR was strongly suggestive of an autocrine or intracrine system for vitamin D action in normal monocytes/macrophages. However, confirmation of such a mechanism was only obtained in 2006 when Robert Modlin and colleagues carried out DNA array analyses to define innate immunity genes that were specifically modulated in monocytes by *Mycobacterium tuberculosis* (*M. tb*). In a seminal investigation both the VDR and the gene for 1α-hydroxylase (CYP27B1) were shown to be induced following activation of the principal pathogen recognition receptor for *M. tb*, toll-like receptor 2/1 (TLR2/1.[23] Subsequent experiments confirmed that precursor $25OHD_3$ was able to induce intracrine VDR responses in monocytes that had been treated with a TLR2/1 activator. In particular, the TLR2/1–$25OHD_3$ combination stimulated expression of the antibacterial protein cathelicidin, so that vitamin D was able to promote monocyte killing of *M. tb*. Notably, the ability to promote expression of the antibacterial protein following a TLR2/1 challenge was directly influenced by the $25OHD_3$ status of the donor serum used for monocyte culture. More recently, scientists have shown that vitamin D supplementation in vivo can also enhance TLR2/1-induced cathelicidin expression. Cathelicidin was identified several years ago as a target for transcriptional regulation by $1,25(OH)_2D_3$-liganded VDR, in that its gene promoter contains a functional vitamin D response element (VDRE).[24] Interestingly, this VDRE occurs within a small interchangeable nuclear element (SINE) sequence which only appears to be present in the cathelicidin gene promoter of higher primates, suggesting that vitamin D regulation of this facet of innate immunity is a relatively recent evolutionary development.[25]

Recent reports have not only underlined the importance of cathelicidin as a target for vitamin D but also suggest that this mechanism may be more complex than initially thought. As yet, the precise signal

system by which TLR activation induces expression of VDR and 1α-hydroxylase remains unclear. Promoter-reporter analysis of the events involved in transcriptional regulation of CYP27B1 suggests that TLR4-mediated induction of the enzyme involves JAK-STAT, MAP kinase and nuclear factor kapa β (NF-κβ) pathways, and that these synergize with IFN-γ mediated induction of CYP27B1.[26] However, other studies have proposed that TLR2/1 induction of 1α-hydroxylase occurs indirectly as a consequence of TLR2/1 induced interleukin-15 (IL-15) which is a potent inducer of CYP27B1 and 1α-hydroxylase activity.[27] In a similar fashion, interleukin 17A (IL-17A) has been shown to enhance $1,25(OH)_2D_3$ mediated induction of cathelicidin, although this response does not appear to involve transcriptional regulation of 1α-hydroxylase or increased VDR sensitivity.[28]

Regulation of the antibacterial protein by $1,25(OH)_2D_3$ has been described for a wide variety of cell types other than macrophages, including keratinocytes, lung, epithelial cells, myeloid cell lines, and placental trophoblasts.[29,30] In some cases, this appears to involve an intracrine response similar to that reported for monocytes. However, the mechanisms controlling local synthesis of $1,25(OH)_2D_3$ in these cells vary considerably. In keratinocytes, low baseline expression of 1α-hydroxylase is enhanced following epidermal wounding by transforming growth factor beta (TGFβ).[31] The resulting rise in $1,25(OH)_2D_3$ concentrations upregulates expression of TLR2 and TLR4 by keratinocytes, thereby priming these cells for further innate immune responses to pathogens or tissue damage. By contrast, in trophoblasts, induction of cathelicidin and subsequent bacterial killing by $25OHD_3$ appears to be due to constitutive 1α-hydroxylase activity, which is not further enhanced by TLR activation. The latter may be due to the rapid non-immune induction of 1α-hydroxylase and VDR which occurs within the placenta during early gestation.[32]

Dendritic cells (DCs) are antigen presenting cells (APCs) are important in initiating CD^{4+} T cells responses. Expression of VDR by purified tissue DCs was first reported in 1987. Subsequent studies using populations of DCs isolated from skin (Langerhans cells) provided evidence that $1,25(OH)_2D_3$ could act to attenuate antigen presentation.[33] In functional studies, $1,25(OH)_2D_3$ treatment of human DCs in vitro results in reduced expression of the cost imulatory molecules CD80 and CD86 and decreased expression of HLA-DR and the maturation marker CD83, all associated with an immature DC phenotype.[34]

Vitamin D inhibits differentiation and maturation of human DCs invitro by suppressing the IL-12 production from DCs and increasing IL-10 production.[35] This is an important immunosuppressive activity as IL-12 is an important cytokine in inducing Th1 development.[34] $1,25(OH)_2D_3$ inhibits the differentiation, maturation, and immune stimulatory capacity of DCs. Canning et al. confirm that $1,25(OH)_2D_3$ suppresses monocyte differentiation into DCs, thereby generating immature DCs. This suppresses DC ability to stimulate T-cell proliferation.[36] Most of the direct immune modulatory properties of $1,25(OH)_2D_3$ on DCs are proposed to occur in myeloid (mDCs) and not plasmacytoid DCs (pDCs). A study by Penna and et al. suggest that although both primary human blood-derived mDCs and pDCs express comparable levels of VDR and upregulate the primary response gene CYP24 upon culture with $1,25(OH)_2D_3$, only the tolerogenic properties of mDCs are modulated upon culture with $1,25(OH)_2D_3$.[37] $1,25(OH)_2D_3$ negatively regulates the differentiation, maturation, and immune stimulatory capacity of DCs by decreasing the expression of MHC class II, CD40,

CD80, and CD86.[38] In addition, $1,25(OH)_2D_3$ decreases the synthesis of IL-6, IL-12, and IL-23.[39]

The other major type of adaptive immune cells, T cells, is also thought to be an important target for the immune modulatory effects of different forms of vitamin D. The development of lymphocytes takes place in the thymus with VDR being expressed in medullary thymocytes but not in the less mature cortical thymocytes. However, once cells leave the thymus and enter the circulation as T or B cells VDR expression is lost until these cells are activated to proliferate by mitogens Indeed, 1,25D is a potent inhibitor of T-cell proliferation, blocking the transition from early G1 phase to late G1 phase, but having no effect on transition from Go (resting) to early G1 or from late G1 to S phase. Weak TCR signaling via the mitogen-activated protein kinase p38 pathway induced VDR expression. The T cells subsequently up-regulated phospholipase C-gamma1 (PLC-γ1) expression 75-fold , enabling them to flux calcium and become fully activated. PLC-γ1 induction appeared to be VDR-dependent. The dependence of T cell activation on VDR expression has not been demonstrated in vivo.[40]

VDR expression by these cells is very low in resting conditions but upon activation and proliferation, T and B cells up-regulate VDR expression significantly, allowing regulation of up to 500 vitamin D responsive genes which influence differentiation and proliferation of these cells.[41] Since 1983 it has been described that $1,25(OH)_2D$ inhibited T cell proliferation and the secretion of select cytokines after mitogen stimulation four potential mechanisms by which vitamin D may influence T cell function have been proposed: 1) direct, endocrine effects on T cells mediated via systemic calcitriol. 2) Direct, intracranial conversion of 25(OH)D to calcitriol by T cells. 3) Direct, paracrine effects of calcitriol on T cells following conversion of 25(OH)D to calcitriol by monocytes or dendritic cells. 4) Indirect effects on antigen presentation to T cells mediated via localized APC affected by calcitriol.

In principle, vitamin D exposure leads to a shift from a pro inflammatory to a more tolerogenic immune status, including very diverse effects on T cell subtypes: Calcitriol suppresses T helper (Th) cell proliferation, differentiation and modulates their cytokine production.[42] In particular, treatment of T cells with calcitriol or analogs inhibits the secretion of pro inflammatory Th1 [IL2, interferon-γ (IFN- γ), tumor necrosis factor α (TNF- α)], Th9 (IL9) and Th22 (IL22) cytokines,[43] but promotes the production of more anti-inflammatory Th2 cytokines (IL3, IL4, IL5, IL10).[44,45] The decrease in the production of IL-2 and IFNγ by $1,25(OH)_2VD_3$ is partially mediated by binding of the VDR–RXR complex to the VDRE in the promoters of genes encoding IL-2. IL17 producing Th17 cells are also affected by vitamin D. Inhibition of Th17 activity seems to play a major role in the treatment of autoimmune diseases as shown in non-obese diabetic (NOD) mice.[46] Recently, calcitriol was found to directly suppress IL17 production on a transcriptional level,[47] and activated human T-cells exposed to calcitriol produced significantly decreased levels of IL17, interferon-γ and IL21.[48] The same study also revealed a change toward a tolerogenic phenotype, including increased expression of genes typicaland regulatory markers FOXP3, CTLA-4, and IL-10 for regulatory T cells (Tregs), by adding a combination of calcitriol and IL2 to human primary T cell cultures. In addition, $1,25(OH)_2D$ upregulated the gut homing receptor CCR9 and inhibited CXCR3 on T cells potentially changing the homing properties of the Th cells.[49] Vitamin D and $1,25(OH)_2D$ inhibited

Th1 and Th17 responses, induced T reg responses, and controlled proliferation and Th cell localization.[39]

INKT cells are also vitamin D targets .Development and function of iNKT cells depends on expression of the VDR and vitamin D.[50,51] In vitro, $1,25(OH)_2D$ inhibited iNKT cell derived IL-17 and induced IL-4 and IL-5. The requirement for the VDR in the development of iNKT cells was traced to regulation of the survival of maturing iNKT cells in the thymus. Vitamin D also controls iNKT cell expansion during development.[51]

Vitamin D has also been proposed as a regulator of Th2 mediated disease such as allergy and asthma. In vitro, $1,25(OH)_2D$ treatment of T cells has been shown to increase IL-4 secretion by human and mouse Th cells.[41,52] IL-13 has been shown to be induced or decreased by $1,25(OH)_2D$ treatment of human T cells.[53] 25-hydroxyvitamin D_3 ($25(OH)D_3$) is the inactive precursor of $1,25(OH)_2D_3$ and is considered the best parameter for evaluation of the vitamin D status of a subject. The normal range of serum $25(OH)D_3$ concentrations is 25–170 Nm.[54] The serum concentration of the active $1,25(OH)_2D_3$ is approximately 1000-fold lower (60–110 pM) and far below the effective concentration of 1,25 $(OH)_2D_3$ found in in vitro studies. Thus, in most in vitro studies more than a 100-fold higher concentration of 1,25 $(OH)_2D_3$ than found in serum is often required to obtain an effect.[55] It has therefore been suggested that the level of circulating $1,25(OH)_2D_3$ is too low to affect immune responses in vivo, and that sufficient levels are obtained by local conversion of $25(OH)D_3$ to 1,25 $(OH)_2D_3$.[10] In accordance, it has been shown that activated antigen presenting cells (APC) express the 25(OH) D-1α hydroxylase CYP27B1 that converts $25(OH)D_3$ to $1,25(OH)_2D_3$, and that APC can produce $1,25(OH)_2D_3$ from $25(OH)D_3$ in vitro and respond to this through the vitamin D receptor (VDR) in an autocrine fashion.[23] Elevated levels of $1,25(OH)_2D_3$ in association with hypercalcemia have been observed in patients with sarcoidosis, tuberculosis, and other infections and inflammatory diseases in which the pathology is characterized by granuloma formation, supporting the hypothesis that activated macrophages can produce significant amounts of $1,25(OH)_2D_3$ in vivo.[56] Like APC, activated T cells express the VDR and CYP27B1.[7] However, whether T cells can convert $25(OH)D_3$ to $1,25(OH)_2D_3$ in physiological relevant concentrations and respond to this in an autocrine fashion is a matter of debate. Most studies on the effect of vitamin D on T cells have not addressed this question as they investigated the direct effects of supra-physiological concentrations of $1,25(OH)_2D_3$ and not how $25(OH)D_3$ affects T cell responses. One study has shown that isolated T cells have the ability to convert $25(OH)D_3$ to $1,25(OH)_2D_3$ in concentrations that actually affect vitamin D responsive genes in an autocrine fashion.[40] In agreement, scientists found that purified CD^{4+} T cells have the ability to produce substantial amounts of $1,25(OH)_2D_3$ when activated in the presence of $25(OH)D_3$.[57] In contrast, another recent study found that although activated T cells do express CYP27B1, the expression level is not sufficiently high to allow production of $1,25(OH)_2D_3$ in concentrations that affect vitamin D responsive genes. The authors found that $25(OH)D_3$ only affected T cell responses when APC were present, and suggested that APC locally secrete sufficient amounts of $1,25(OH)_2D_3$ to directly influence the surrounding T cells in a paracrine fashion. Other important players influencing the bioavailable levels of vitamin D are the vitamin D-binding protein

(DBP) and albumin. $25(OH)D_3$ and $1,25(OH)_2D_3$ circulate bound to DBP (85–90%) and albumin (10–15%) with less than 1% in their free form.[58] Studies of DBP knock-out mice have shown that DBP acts as a vitamin D reservoir by protecting $25(OH)D_3$ and $1,25\ (OH)_2D_3$ from degradation and renal secretion.[15] However, DBP also sequesters $25(OH)D_3$ and $1,25(OH)_2D_3$ and inhibits their action on monocytes, DC and keratinocytes in vitro.[15] How DBP affects T cell responses to $25(OH)D_3$ still needs to be determined. The objectives of this study were to further elucidate whether T cells have the ability to convert $25(OH)D_3$ to $1,25(OH)_2D_3$ in proportions that affect a panel of vitamin D responsive genes in an autocrine fashion and to investigate how DBP regulates T cell responses to $25(OH)D_3$.

Like T-cells, active but not inactive B-cells express the VDR. Consequently, initial studies indicated that $1,25(OH)_2D_3$ could directly regulate B-cell proliferation and immunoglobulin (Ig) production.[59] In B-cells, anti-proliferative effects of calcitriol such as inhibition of differentiation, proliferation, initiation of apoptosis and decreased immunoglobulin production were initially considered to be exclusively indirectly mediated by T helper (Th) cells.[60] expression of CYP27b1 was also detected in B-cells, indicating that B cells may be capable of autocrine/intracranial responses to vitamin D. More recent studies confirmed additional direct effects of calcitriol on B cell homoeostasis, including inhibition of memory- and plasma-cell generation, as well as promotion of apoptosis of immunoglobulin-producing B cells.[61] This control on B cell activation and proliferation may be clinically important in autoimmune diseases as B-cells producing auto reactive antibodies play a major role in the pathophysiology of autoimmunity.[12]

Autoimmune diseases are characterized by a loss of immune homeostasis resulting in corrupted self-antigen recognition followed by the destruction of body tissue by auto reactive immune cells. A combination of genetic predisposition, epidemiological risk factors,[62] and environmental contributors contributes to the development of autoimmune diseases. One important factor may be the availability of sufficient vitamin D levels as various epidemiological studies suggest associations between vitamin D deficiency and a higher incidence of autoimmune diseases, such as T1D, MS, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD).[63]

In animal models for T1D, MS, SLE, IBD and autoimmune uveitis, administration of calcitriol either prevented or ameliorated autoimmunity. Studies with vitamin D deficient or VDR knock-out animals show increased inflammation and susceptibility to T1D and Crohn's disease, disturbed T cell homing and lack of host protection from bacterial invasion and infection.[64]

Serum 25(OH)D is considered the most accurate marker for vitamin D status.[65] While the Endocrine Society advocates that levels below 20 ng/mL (50 nmol/L) should define deficiency, levels ranging from 20 to 29.9 ng/mL (52–72 nmol/L) should define insufficiency and levels above 30 ng/mL (75 nmol/L) should define sufficiency, the Institute of Medicine (IOM) considers levels of >20 ng/mL to be sufficient for the majority of the general population.[49] This latter classification is based largely on vitamin D's effects on bone and mineral homeostasis. The optimal 25(OH)D serum level regarding other aspects of human health is still under debate.[66] For immune-mediated diseases, experts suggest that even higher serum 25(OH)D levels may be needed to lead to positive effects.[67]

Calcitriol is well known for its diverse pharmacological activities, including modulation of cell growth, neuromuscular and immune function and reduction of inflammation. Calcitriol and its analogs exert potent effects on cellular differentiation and proliferation regulate apoptosis and produce immune modulatory effects.[68]

Vitamin D has several important roles in the skin. Many in vitro and in vivo studies demonstrate dose-dependent effects of vitamin D on cell proliferation and differentiation.[11,69] Although the mechanisms that mediate the anti-proliferative and pro-differentiating effects of vitamin D analogs on keratinocytes are not completely understood, it is well known that these effects are at least in part genomic and mediated by VDRs (1,25-dihydroxyvitamin D_3).[11] Vitamin D can reduce the risk of skin infection through modulating the production of various antimicrobial peptides and the cytokine response.[70] It is possible that vitamin D could enhance T helper type 2 responses. Vitamin D deficiency is related to a high number of skin disorders, including skin cancer, autoimmune skin disorders, photo dermatoses, atopic dermatitis and psoriasis. Vitamin D and its analogs have already been successfully used in the therapy of atopic dermatitis, psoriasis, vitiligo, acne and rosacea.[71] Most of the studies are devoted to treatment of psoriasis. The highly variable nature of psoriasis and its individual presentations in patients can make choosing the most appropriate treatment difficult. Currently available synthetic vitamin D analogs that have been found to be safe and effective in topical treatment of psoriasis include calcipotriol (or calcipotriene), max-acalcitol, tacalcitol and hexafluoro-1a, 25-dihydroxyvitamin D_3.[72] According to the literature, the rate of treatment success with vitamin D and its analogs varies from 4% to 53%,[73] and many of them have significant adverse effects. Calcipotriol is considered as a highly effective topical agent for the treatment of hyper proliferative skin diseases, such as psoriasis.[74] Calcipotriol exerts only negligible systemic effects on calcium homeostasis. Thus, eliminating the risk of the main significant side effects of hypercalciuria, hypercalcemia and bone calcium mobilize.[75]

The role of vitamin D and its analogs in cancer treatment and prevention was investigated in different research tracks including clinical and epidemiological studies. According to extensive epidemiological research reports,[64] it was found that there is a clear association between various factors responsible for vitamin D levels in the body (e.g. geography and latitude, history of sun exposure, lifestyle) and increased morbidity from cancer. It was also found that vitamin D and its analogs inhibit proliferation of cancer cells derived from multiple tissues.[76] Further studies are required to clarify the molecular mechanisms of the anticancer activity of vitamin D and its various analogs. From the current literature on the subject, it appears that the compound is not suitable for use in cancer as a single or primary anticancer agent but as an adjuvant in combination chemotherapy, where it can aid the actions of other cytotoxic agents, particularly those of the alkylating agents (which are not cell cycle specific). The anticancer vitamin D analogs include new calcipotriol-derived compounds, diastereomeric and geometric analogs of calcipotriol, seocalcitiol, 20-hydroxyvitamin D_2 analog, 5-butyloxazole unit analog and additional analogs containing a structurally modified side chain.[77-79] The dominant side effects of vitamin D, hypercalcemia and hypercalciuria, resulted in limiting the use of vitamin D in cancer treatment.[80] To overcome this problem, more than 3000 vitamin D analogs have

been synthesized in recent years.[81] Some of these analogs have been found to be more effective and less toxic than vitamin D, justifying their development and introduction to the market.[82] BGP-13 and BGP-15, calcipotriol derived vitamin D_3 analogs, are good examples of more-effective and less-toxic analogs than vitamin D.[76] BGP-15 is a calcipotriol-based analog where the 24-OH has been substituted by a chloride atom on the side chain of the calcipotriol molecule. BGP-13 and BGP-15 have been shown to induce apoptosis and inhibit prostate and breast cancer growth in vitro and in mice in vivo.[77] Antitumor effects of vitamin D and its analogs were also demonstrated in humans, when they were used either alone or in combination with other chemotherapy drugs Vitamin D activity is expressed also by causing tumor regression and inhibition of tumor growth, in addition to counteracting their mutagenic effect by inducing apoptotic cell death. Some evidence suggests that this vitamin could be used in high doses as a prophylactic agent for prevention of colorectal, prostate and breast cancer development. Only large-scale long-term research will reveal which vitamin D analogs, either alone or in combination with other drugs, could serve as effective therapeutic agents for cancer.[83]

Type 1 diabetes is an autoimmune disease characterized by the immune-mediated destruction of insulin-producing b cells from islets of Langerhans in the pancreas. As mentioned above, vitamin D plays a vital part in the normal functioning of the immune system and its deficiency could lead to impaired functioning of the immune system. It was shown that vitamin D mediates insulin secretion and glucose uptake,[84] and also regulates insulin receptor gene expression. Epidemiological studies have shown a direct correlation between the increase in the prevalence of the disease and deficiency of vitamin D. The ability of a potent vitamin D analog: 2α-Methyl-19-nor-(20S)-1,25-dihydroxyvitamin D_3 (2AMD), to prevent type 1 diabetes was determined in an Ins2/non-obese diabetic (NOD) model. 2AMD suppresses development of type 1 diabetes, preserves islet cells and has a significant impact on B cell survival and function.[85] A detailed mechanism of antidiabetic activity of vitamin D in type 2 diabetes is unclear Lifestyle factors leading to type 2 diabetes, including obesity, aging and lack of physical activity. It can also cause vitamin D deficiency. It is only known that vitamin D regulates direct and indirect action on insulin-producing cells in the pancreas. Vitamin D can directly influence the muscle and fat cells, and can improve insulin action through reducing insulin resistance as well as reducing inflammation which is commonly present in patients with type 2 diabetes.[86] A small-scale post hoc analysis of a bone study revealed that daily calcium (500 mg) and vitamin D (700 IU) supplementation for three years prevented a further rise in fasting blood glucose in a subgroup with impaired fasting blood glucose (100–125 mg/dl) at a baseline.[87]

Multiple Sclerosis (MS) is a chronic and a common inflammatory disorder of the central nervous system (CNS) characterized with myelin loss, progressive neurological dysfunction, gliosis, and unstable degrees of axonal pathology that initiated by auto reactive T cells that recognize central nervous system antigens.[88] Various genetic and environmental risk factors appear to interact and contribute to MS. In genetics, several human leukocyte antigen alleles (more particularly HLA-DRB1*1501) could favor the disease whereas others could be protective. Some of the genes involved in vitamin D metabolism (e.g. CYP27B1) also have a significant role in MS.[89] Based on epidemiological studies, three environmental risk factors were identified: 1) previous

Epstein-Barr virus infection 2) vitamin D insufficiency 3) and cigarette smoking. Some clinical findings strongly suggest that vitamin D status influences the relapse rate and radiological lesions in MS patients. It was suggested that changes in vitamin D serum concentrations are correlated with MS.[90] Although the results of adequately powered randomized clinical trials using vitamin D supplementation have not yet been reported, vitamin D is a promising candidate as modulator of disease activity in MS.

Vitamin B is recognized as a family comprising eight different members. All of B vitamins are water-soluble, and they are involved in various pathways of cell metabolism. Vitamin B is essential for the synthesis, replication, and repairing of nucleotides for DNA and RNA and is thus required for cell proliferation and survival. Vitamin B_9 deficiency also inhibits the activity of CD^{8+} T cells and reduces the proliferative responses of lymphocytes and natural killer cell activity; in turn ,this inhibition is associated with decreased resistance to infections. Consequently, vitamin B6 deficiency leads to various impairments of immunity, such as lymphoid atrophy and reduced numbers of lymphocytes (3); conversely, vitamin B6 supplementation bolsters these weakened immune responses. Like vitamin B6, vitamin B9 (also known as folate and folic acid) is essential for nucleic acid and protein synthesis,[91] and in adequate levels of vitamin B9 dramatically alter the immune response. Among the vitamins B, vitamin B6 is essential for metabolism of nucleic acids, amino acids, and lipids and thus influences cell growth Vitamin B9 is derived from both diet and commensal bacteria.[92] Additionally, the vitamin B9 receptor folate receptor 4 (FR4) is both a marker of Treg cells and is immunologically functional.[93]

Folate receptor 4, a vitamin B9 receptor, is highly expressed on the surfaces of Treg cells, implying a specific function of this vitamin in these cells. In particular, recent study revealed that vitamin B9 is crucial in the maintenance of Treg cells. In the absence of vitamin B9, naive Tcells can differentiate in to Treg cells, but differentiated Treg cells fail to survive owing to the decreased expression of anti-apoptotic molecules (Bcl-2).[93,94]

A recent study demonstrated an additional function of the vitamin B family in the control of immune responses via mucosa- associated invariant T (MAIT) cells. MAIT cells are unconventional T cells that express a semi-invariant αβ T cell receptor that is restricted by the MHC class I-related molecule MR1. These cells are mostly found in the intestine, liver, and lung.[65] Because MAIT cells can react rapidly to bacterial infections (e.g. *Escherichia coli*, *Klebsiella pneumoniae*, and *Mycoplasma tuberculosis*), it was supposed that the antigen presented to MR1 was bacteria-derived molecules. However, a recent study clarified that, in fact, bacterially produced metabolites of vitamin B9 and vitamin B2 bound to MR1 are presented as antigen to MAIT cells. Furthermore, like vitamin B2 derivatives, the vitamin B9 metabolite, and 6-formyl pterin. (6-FP) bind to MR1 but, unlike vitamin B2 derivatives, fails to activate MAIT cells.[96] These findings suggest that, depending on their metabolism by commensal bacteria and presentation by MR1, members of the vitamin B family can act either as positive or negative regulatory ligands for MAIT cells.[97]

CONCLUSION

Clinical evidence has long indicated that in adequate vitamin intake disrupts host immunity. Thus, they predispose humans to infectious and inflammatory diseases. Accumulating evidence has revealed the

molecular and cellular mechanisms underlying myriad functions of vitamins in innate and acquired immune responses. Growing interest exists in the physiologic role of vitamin D as an essential mediator in maintaining a healthy and functional immune system. The active form of vitamin D $1,25(OH)_2D_3$ influences innate and adaptive immunity. It acts on APCs and T cells to promote peripheral tolerance via inhibition of inflammatory responses and induction of Tregs. Vitamin B9 is crucial for the maintenance of Treg cells. Intriguingly, vitamin B9 was required for the survival of differentiated Treg cells, but was not necessary for the differentiation of naive T cells into Treg cells. As the mechanism of FR4-mediated Treg-cell maintenance, scientists considered initially that the proliferative activity of Treg cells could require large amounts of vitamin B9 as a source of nucleotides for DNA and RNA. However, the amounts of intracellular vitamin B9 were identical between Treg and non-Treg cells, implying that FR4 specifically recognizes extracellular vitamin B9 for the maintenance of Treg cell survival, consistent with a report that FR4 expressed on Treg cells contributes to their immune function and survival. The complex functions of vitamins in the regulation of the immune system efforts likely will enable scientists to refine our understanding of the mechanisms underlying the immunologic roles of various vitamins and to advance the development of vitamin-dependent therapeutic agents for the control of infectious and immune diseases. These findings clarify the beneficial roles of vitamins in the maintenance of immunologic homeostasis and inform the design of vitamin analogs as pharmacologic agents for the generation and maintenance of a healthy immune condition.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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