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REVIEW ARTICLE

Role of Active Vitamin D3 in Immunity

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ABSTRACT

Introduction: The active vitamin D3—1,25 dihydroxy cholecalciferol—is the key player in calcium and phosphorus metabolism and skeletal growth and functions. However, recent new developments have revealed its role in other tissues as well, referred to as the nonclassical actions of vitamin D. Not only the endocrinal effects, evidence indicates that vitamin D3 also has autocrine and paracrine functions due to its extrarenal synthesis by many cells, including the immune cells. All cells of the immune system have vitamin D receptors and show wide-ranging effects to it. It impacts both the innate and adaptive immune systems and the overall influence points to anti-infective, anti-inflammatory, immunosuppressive, and regulatory roles. It shows a significant role in chronic inflammatory and autoimmune diseases as well in susceptibility to infections.

In this review, newer developments on the role of vitamin D in immunity and the underlying mechanism are discussed with possible future reflections.

Keywords: Active vitamin D3, Adaptive immunity, Calcitriol, Immunity, Innate immunity.

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INTRODUCTION

Vitamin D has been synonymous with bone health and disease for a very long time. However, now, it is recognized as a pleotropic hormone with multiple roles on many tissues and organs. More than 25 years ago, vitamin D was touted as an immunomodulator based on the findings that macrophages and monocytes from the patients of sarcoidosis synthesized $1,25(OH)_2D3$ from its precursor 25 hydroxy cholecalciferol. Only recently, its crucial role as a potential immune modulator has been recognized. Clear identification of its well-documented roles in immune response and autoimmunity has led it to being actively pursued as a potential therapeutic agent.[1,2]

Vitamin D3 influences all the key cells of the immune system and produces intracrine and paracrine effects on them. Most immune cells have the enzyme system to produce the active form of vitamin D3. It is an inhibitor of differentiation and maturation of dendritic cells (DCs) and decreases their antigen-presenting activity. It acts directly on T cells and alters the profile of their proliferation and differentiation. It promotes anti-inflammatory environment by inhibiting the Th1 and Th17 cells and promoting the Th_2 and T_{reg} cell differentiations. Further, vitamin D3 represses the transcription of the key pro-inflammatory Th1 cytokines like interferon (IFN)-γ and interleukin (IL)-2. The B cells show significant changes under the influence of vitamin D3, including the differentiation into plasma cells and memory cells and the secretions of immunoglobulins.[2]

Vitamin D3 induces antimicrobial effects in monocytes/macrophages by enhancing their phagocyte activity as well as helping the synthesis of antimicrobial peptides. Sunlight-mediated epidermal expression of $1,25(OH)_2D3$ acts as the link between the environment and immune system. It induces suppression of cutaneous immune response through the T-regulatory cells. Overall, it is considered an important regulator of both innate and adaptive immune systems. There is an emerging view that the vitamin D deficiency, which is widely prevalent these days, could have an important role in immune disorders, especially the autoimmune diseases.[2]

In this review, we present an overview of the current knowledge on vitamin D as an immunomodulator with the underlying molecular mechanisms and its possible role in immunological response with future implications.

VITAMIN D—THE MOLECULE

Ergocalciferol, vitamin D2, and cholecalciferol, vitamin D3, are the two major forms of vitamin D. Vitamin D2 is synthesized by plants and fungi, while vitamin D3 is produced in large quantities in humans by photosynthesis in the skin. The ultraviolet (UV) light falling on the skin catalyzes the conversion of 7-dehydro-cholesterol into the previtamin D, which then spontaneously

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isomerizes into cholecalciferol. This is bound by the vitamin D-binding protein (DBP) and transported to the liver. To act biologically, vitamin D3 is hydroxylated at two positions—first at the 25th position in the liver catalyzed by 25 hydroxylase to make 25 hydroxy D3 (25-OH D3). Many isoforms of this 25 hydroxylase, also called cytochrome 450, are known, including the mitochondrial CYP27A and microsomal CYP2R1, CYP3A4, etc. But, the high-affinity CYP2R1 is the most active. This 25-OH D3, also called calcidiol, is transported to kidneys where renal tubules catalyze the second hydroxylation at the 1st position by 1-alpha hydroxylase (CYP27B1) to form $1,25(OH)_2D3$, or calcitriol, the active form of vitamin D3.[1]

Another hydroxylase, CYP24A1, converts both 25-OH D3 and $1,25(OH)_2D3$ into less active $24,25(OH)_2D3$ and $1,24,25,(OH)_3D3$ respectively. The level of $1,25(OH)_2D3$ is mainly determined by the balance between CYP24ndA1 and CYP27B1. Fibroblast growth factor 24 (FGF24) and parathyroid hormone (PTH) are important in this regulation. High $1,25(OH)_2D3$ and low phosphate levels induce FGF24, which shifts the balance toward inactive metabolites through CYP24A1. Low calcium level stimulates PTH secretion, which shifts the balance toward CYP27B1, leading to vitamin D activation and signaling. Calcitriol is released into the bloodstream to produce a large number of physiological actions.[2] Vitamin D3 synthesis in skin is the major source of vitamin D in humans and this form is more active than D2. It is also more effective in maintaining the 25-OH D3 levels in serum,[3] the marker of vitamin D status in humans.

VITAMIN D3—THE SIGNAL PATHWAYS

The action of vitamin D3 is by binding to a specific vitamin D3 receptor (VDR) and retinoid X receptor (RXR) in the nucleus of various cells in the body. The VDR is a member of a family of nuclear receptors and acts as a ligand-activated transcription factor. It is present in many cells, including the cells of the immune systems.[2] This complex binds to specific deoxyribonucleic acid (DNA) sequences called vitamin D response elements (VDREs). Structurally, VDR has a highly conserved DNA-binding domain and an alpha helical ligand-binding domain. Ligand binding induces a conformational change in the VDR, leading to the formation of two new protein interaction surfaces. One is for binding of RXR to form the VDR–RXR heterodimer for specific binding to VDREs. The other binding surface is for various coregulatory proteins leading to genomic effects.[3] This activated complex recruits vitamin D receptor interacting protein complex[4] and several other coactivator and coregulatory proteins to influence several mechanisms like histone modifications, chromatin modeling, ribonucleic acid (RNA) polymerase II binding, etc. It also induces the exchange of several coactivators and repressors in the transcriptional complex of VDR responsive promoters. It may also involve epigenetic changes like VDR-induced DNA methylation.[5] The $1,25(OH)_2D3$ signaling may involve several pathways mediated through protein kinase C, phosphatidylinositol 3 kinase, the calcium-dependent and mitogen-activated protein kinases, etc.[6]

This vitamin D3-induced signaling requires sufficient concentrations of vitamin D3 in blood and its subsequent binding to DBP for transport to the different cells in the body. Classical targets like parathyroid gland and osteoblasts also express significant CYP27B1 activity, besides VDR expression.[7] This indicates a localized synthesis of calcitriol and an intracrinal effect rather than the endocrinal response. Cell and tissue-specific expression of CYP27B1 by calcitriol may involve several mechanisms and numerous VDREs found in the promoter proximal regions. It is not fully established if calcitriol-mediated activation leads to any modification in VDR protein, though some studies point to its phosphorylation. Similarly, its fate following $1,25(OH)_2D3$-induced activation is not fully established, both in the ligand bound and unbound forms. It is not known if it is translocated to the nucleus or if it continually shuttles between cytosol and nucleus or if it is trapped inside the nucleus.[8]

VITAMIN D3 AND IMMUNE CELLS

The VDRs are found on most immune cells like monocytes, macrophages, DCs, B cells, T cells, etc., and vitamin D has pleotropic effects on the immune system.[9] The VDR activation and signaling in immune cells were shown to result in the antiproliferative, prodifferentiation, and immunomodulatory effects. Vitamin D3 has suppressive effects on NF-kB signaling pathways in T cells, monocytes, and macrophages,[10] but not in B cells. Similarly, the transcription of many other regulatory factors by $1,25(OH)_2D3$ has been evaluated. All these finding indicate the differential actions of vitamin D3 on these cells.

VITAMIN D3 AND MONOCYTE/MACROPHAGES

One of the earliest studies linking vitamin D3 and immunity was the enhancement of antibacterial response of monocytes and macrophages by $1,25(OH)_2D3$. Recently, the monocytes/macrophages isolated from sarcoidosis granuloma or from the alveolar levage fluid were shown to have 1α hydroxylase activity capable of synthesizing $1,25(OH)_2D3$ from 25-OH D3.[11] Subsequently, this was shown in other granulomatous diseases and cancers also.[12]

Human peripheral blood mononuclear cells also synthesize $1,25(OH)_2D3$ in response to immune stimuli, such

as IFN-γ or bacterial antigens agonists of TLRs, such as lipopolysaccharides. Both these stimuli induce the expression of CYP27B1 in activated macrophages.[13] In culture studies of human macrophages, increased antimicrobial activity has also been demonstrated following TLR stimulation with lipopolysaccharides. African-Americans, who are more prone to tuberculosis, had low 25-OH D3 levels and were less efficient in antimicrobial activity induction. This was in contrast to white Americans who had higher vitamin D3 levels.[14] Treatment of human monocytes with $1,25(OH)_2D3$ not only suppresses the expression of both TLR-2 and TLR-4 in a dose- and time-dependent manner, but also promotes the antimicrobial activity of the myeloid cells. This appears contradictory and results in a state of hyporesponsiveness.[15] Subsequently, it was found to be part of a negative feedback mechanism, which prevented the excessive TLR activation and inflammation in the later stage of infection. This could be brought about by calcitriol by decreasing or preventing the release of inflammatory cytokines by the macrophages. Calcitriol directly induces the expression of other innate pathogen recognition receptors like NOD2/CARD15/IBD1 in monocytes and leads to the expression of antimicrobial peptide defensin β2 through NF-kB pathway after activation by their natural ligands.[16] Prolonged signaling in macrophages is induced and maintained over an extended period by $1,25(OH)_2D3$ and is considered advantageous for combating the intracellular pathogen like *Mycobacterium tuberculosis*.[17] It is explained based on the presence of defective negative feedback loop mediated in macrophages by an alternatively spliced and inactive variant of 24 hydroxylase.[18] Signaling also suppress the induction of matrix metalloproteinase 7, 9, and 10 in peripheral blood mononuclear cells infected with *M. tuberculosis*.[19] Calcitriol also enhances the secretion of IL-10, prostaglandin E-2, and the antibacterial peptide cathelicidin[20] in human myeloid cells. This peptide has a direct antimicrobial and antiviral effect on the invading organisms. This localized synthesis of $1,25(OH)_2D3$ promotes pathogen killing and may also involve induced nitric oxide, iNO.[21]

VITAMIN D3 AND DCs

Different subsets of DCs have different origins, phenotype, and functions being derived from both myeloid precursors, the myeloid DCs (mDCs) and from lymphoid precursors, the plasmacytoid DCs (pDCs). They produce cytokines and have a critical role in T-cell responses. The mDCs are important as antigen-presenting cells (APCs) while pDCs are involved with the immune tolerance.[22] Tissue-extracted immature DCs express VDRs, but this expression decreases in mDCs during their differentiation into mature DC. Contrary to this, CYP27B1 expression increases during the differentiation.[23] So, mature DCs are not much responsive to $1,25(OH)_2D3$, but they become capable of endogenous synthesis of vitamin D3.

In Langerhans DCs derived from skin, $1,25(OH)_2D3$ attenuates their function as APC.[24] Further, treatment of mDCs with $1,25(OH)_2D3$ suppresses the maturation of DCs and expression of major histocompatibility complex II, CD40, CD80, and CD86 molecules needed for the initiation of T-cell response. In addition, it also suppresses the expression of maturation proteins and synthesis of IL-6, IL-1, and IL-23.[23] The maturation of mDCs in presence of $1,25(OH)_2D3$ induced by lipopolysaccharides results in their becoming tolerogenic. If the anergic T cells are treated with immature DCs primed with calcitriol, they express $FoxP^3$ and become T_{reg} cells. These T_{reg} cells are fully competent in mediating tolerance to transplants and arresting the development of autoimmune disorders.[25]

Most of these effects are shown in *in vitro* studies using very high exogenous and nonphysiological doses of vitamin D3. It role is doubtful at physiological concentrations. It is argued that the local intracrine synthesis of $1,25(OH)_2D3$ may be effective in achieving these responses. The vitamin D3 exerts its effects on human mDCs by inhibiting the activation through NF-kB.[26] The plasmacytoid DCs show similar response and vitamin D3 synthesized by them promotes tolerance through paracrine effects on VDR-positive T cells.

VITAMIN D3 AND B CELLS

Human primary B cells constitutively express VDRs at low levels, which are upregulated on stimulation in presence of vitamin D3.[27] The CYP27B1 messenger RNA is also expressed by resting B cells in humans, and it is further enhanced on their stimulation, but vitamin D3 has no effect. Instead, significant upregulation of CYP24A1 is seen in B cells after incubation with $1,25(OH)_2D3$. This enzyme converts 25-OH D3 into inactive $24,25(OH)_2D3$ and is unaffected by stimulation of B cells directly. So, the vitamin D action on B cells is likely to be due to VDR upregulation and its inactivation by CYP24A1 on stimulation.

Addition of 25-OH D3 to the purified B cells stimulated by anti-CD40 Abs and IL-21 led to the inhibition of proliferation of activated B cells, their differentiation into plasma and memory cells, and IgG production by them. It is now clear that human B cells can take up 25-OH D3 and convert it into $1,25(OH)_2D3$, which then inhibits the B-cell functions.[28] Vitamin D3 inhibited the proliferation of activated B cells directly by influencing the expression of cell cycle genes like CDK4, CDK6, and cyclin D. The vitamin D3-induced inhibition of proliferation was associated with the apoptosis of activated B cells.[28]

This could explain the altered vitamin D_3 metabolism in systemic lupus erythematosus in which there is diffuse B-cell activity.[29] These results suggest that major effect of $1,25(OH)_2D3$ on B cell is the reduction in proliferation of activated B cells, differentiation into plasma cells, and reduced secretion of antibodies.

VITAMIN D3 AND CD4+ T CELLS

The VDR expression in resting T cells is very low than the activated $CD4^+$ T cells where it is increased by tenfold.[30] However, the native T_H cells are VDR-negative and responded poorly to *T-cell receptor* (TCR) stimulation *in vitro*. It was then found that VDR expression was needed for optimal human T-cell activation. The VDR binds to calcitriol, translocates to the nucleus, and activates T cells fully. Vitamin D controls the TCR-mediated signaling and activation in human T cells. Vitamin D_3 influences T_H cells in many ways. It alters cytokine secretion, suppresses effector T-cell activation, induces T_{reg} cells, and affects migration of T cells to specific tissues like lymph nodes, gastrointestinal tract, skin etc., through chemokine and chemokine receptors interaction.[31] The effects of vitamin D3 differ on various T_H cell subsets are given below.

T_H1 AND T_H2 CELL DIFFERENTIATION

Vitamin D_3 modifies the T_H cell differentiation and phenotype, preferentially inhibiting T_H1 differentiation associated with cellular immune response and promotes T_H2 shift as demonstrated by the cytokine profile of calcitriol-treated human T cells. It inhibited the T_H1 cell proliferation and production of IL-2, IFN-γ, tumor necrosis factor (TNF)-α, and IL-5.[32] Calcitriol also induced transforming growth factor (TGF)-β and IL-4 expression indicating T_H1-suppressive and T_H2-enhancing effects.[31,33] This T_H1 cell response is blunted by promoting the production of tolerogenic DCs that promote T-suppressive action.[34] The VDR expression on $CD4^+$ T-cell subsets has also been shown in rodents[35] and humans.[30]

T_H17 CELLS

T_H17 cells are a subset of $CD4^+$ T cells, which play an important role in immune response. They have a central role in many inflammatory and autoimmune diseases. Accumulated reports indicate the anti-inflammatory role of calcitriol on these cells. The T_H17 cells produce IL-17A, IL-22, IL-21, TNF-α, and IL-6. Secretion of IL-17F is limited and IL-17A is the main cytokine of the IL-17 family (IL-17A to IL-17F). Experimental studies indicate that IL-6 and TGF-β promote T_H17 cell development, while IL-23 is needed for their maintenance. Orphan nuclear receptor (ROR γt) is a master regulator guiding the T_H17 cell differentiation.[36] The IL-17 secretion is upregulated in inflammatory and autoimmune diseases and synergizes with TNF-α to promote the inflammatory state.[37]

Differentiated T_H17 cells express VDRs and calcitriol has shown an immunosuppressive effect. Calcitriol also suppresses the role of DCs in priming the T_H17 cells, commitment of $CD4^+$ cells to T_H17 lineage and IL-17 secretion by them.[38] The TGF-β induces the $Foxp3^+$ T_{reg} cells differentiation of CD^+T cells, but in additional presence of IL-6, Th17 cell differentiation is promoted.

The $1,25(OH)_2D3$ suppresses the production of IL-6 and IL-17 in human PBMCs stimulated with *Candida albicans*,[39] inhibits theT_H17 cells differentiation in rheumatic arthritis,[40] and decreases IL-17 mediated experimentally induced acute colitis in mouse model.[41] Further, TGF-β1 has a dose-dependent response on T_H17 cells differentiation, which is promoted at lower concentrations and suppressed at higher concentrations through the modulation of Foxp3 expression.[42] All these studies confirm the suppression of T_H17 cell development by calcitriol through the upregulation of TGF-β1.

Recent studies indicate that all T_H17 cells are not pathogenic.[43] In fact, TGF-β1- and IL-6-induced T_H17 cells are not pathogenic and do not induce tissue inflammation unless they are further exposed to IL-23. This is critical for TGF-β1 expression and pathogenicity. Further, the inhibition of IL-23 by calcitriol results in decreased inflammation in an animal model.[41] The T_H17A secretion is regulated at the transcription level and calcitriol suppresses it as well as T_H17 cell function.[44] Human studies including cell culture with calcitriol and vitamin D_3 supplementation resulting in higher serum levels have shown reduction in T_H-17 cells.[45] However, the findings are not equivocal and conflicting in human studies.[46]

T_{REG} CELLS

The T_{reg} cells are defined functionally by their ability to suppress and limit the overactivation of effector T cells and, thereby, prevent autoimmune diseases.[47] There are several types of them and $CD4^+$ $FoxP^{3+}$T cells are the most intensely studied. One of these $CD4^+$ $FoxP^{3+}$ cell subsets arises from the thymus called thymic or natural T_{reg} cells (nT_{reg}) and another arises during TCR engagement in the periphery, the peripheral or induced T_{reg} cells (iT_{reg}).[48]

Upon activation by CD3 stimulation and costimulation with compliment regulator CD46 in presence of IL-2, $CD4^+$ T_{reg} cells undergo rapid proliferation and secrete large amounts of IL-10 and TGF β to induce immune suppression.[49] They also induce APC cell lysis through granzymes leading to T-cell activity termination.

Ground-breaking animal model studies showed the involvement of calcitriol in T_{reg} cell activity. The UV

exposure of skin enhanced the immunity to pathogens and induced peripheral tolerance by promoting iT_{reg} cell development through a calcitriol- and VDR-dependent mechanism in keratinocytes, which have a complete vitamin D metabolism capability.[50] In animal studies, cutaneously applied calcipotriol, a synthetic vitamin D analog, mimicked cutaneous UV exposure and led to the IL-10 producing T_{reg} cells by similar mechanism.[51]

The IL-10 is an important anti-inflammatory cytokine that protects many tissues from immune-mediated pathology.[52] Disruption of IL-10 and 1L-10R signaling results in inflammatory diseases.[53] Studies in animals suggest that the calcitriol-dependent development of IL-10 producing T_{reg} cells requires the functional *vdr* gene in $CD4^+$ T cells.[54] But, there is limited information on this link of increased IL-10 synthesis induced by calcitriol in humans. There are reports supporting it[55] and contradicting it.[30] A recent *in vitro* study has demonstrated the increased IL-10 production by lymphocytes following the calcitriol synthesis in a VDR-dependent manner. Further, it is seen that addition of calcitriol in cultures at low concentrations (10^{18}moles/L) increases the frequency of $CD4^+IL\text{-}10^+T_{reg}$ cells, while at higher concentrations (10^6 moles/L) increases the frequency of $CD4^+FoxP^{3+}T_{reg}$ cells. But, there is little coexpression of both types of cells.[56] Addition of TGF-β with calcitriol favored the $CD4^+FoxP^{3+}$cells. Both these cell populations are immunosuppressive, acting through IL-10-dependent and independent mechanisms.

Studies of $CD4^+FoxP^{3+}T_{reg}$ cells in humans are limited. Blood levels of 25-hydroxy vitamin D3 have shown correlation with the $CD4^+FoxP^{3+}T_{reg}$ cells in two studies[57,58] and their suppressive activity in multiple sclerosis (MS) patients.[46] Contradictory results were seen in infants whose 25-OH D3 levels did not correlate with the T_{reg} cells.[59]

VITAMIN D3 AND $CD8^+$ T CELLS

The $CD8^+$ T cells, on activation, produce main effector cells of cellular arm of adaptive immunity to eliminate abnormal cells like those with infections, cancers, and genetic abnormalities by inducing apoptosis. In addition, they produce cytokines, which modify the activity of other immune cells.[60]

The $CD8^+$ T cells also express high levels of VDRs than the $CD4^+$ T cells. Vitamin D3 induces quiescence of $CD8^+$ T cells through a VDR-mediated signaling and prevent their hyperactivation with subsequent tissue damage. Adoptive transfer of $VDR^{-/-}$ $CD8^+$ T cells in the Recombination Activating Gene-deficient mouse induces intestinal inflammation. Further, when $VDR^{-/-}$ $IL10^{-/-}VD8^+$ cells are transferred, the inflammation becomes worse.[61] In addition to maintaining the $CD8^+$Tc cell quiescence, $1,25(OH)_2D3$ also inhibits the secretion of IFN-γ and TNF-α by the activated $CD8^+$ T cells.[62] Topical application of calcipotriol decreases the frequency of $CD8^+$ $IL\text{-}17A^+$T cells in psoriatic lesion.[63]

The $CD8^+$ T cells also contribute to the pathogenesis of autoimmune disease even though their role is not as clear as of $CD4^+$ T cells. Myelin-specific $CD8^+$ T cells induce experimental allergic encephalomyelitis (EAE) in mice, which resembles multiple sclerosis in humans. Similarly, hsp-60 specific $CD8^+$ T cells induce intestinal inflammation. Recently, $CD8^+IL\text{-}17A^+$ cells are abundantly found in synovial fluid of psoriatic arthritic patients and show positive correlation with disease activity.[64] However, $CD8^+$ T cells do not mediate the effect of vitamin D3 in all the autoimmune diseases. For example, they are dispensable in attenuation of EAE by vitamin D3.

UNCONVENTIONAL T CELLS

Mucosa-associated invariant T cells (MAIT), γδ TCR^+T cells, and natural killer (NK)T cells are called as unconventional T cells because they do not express either CD4 or CD8 like the usual T cells. The MAIT cells are believed to be immuno-suppressive as far as autoimmunity is concerned.[65] However, the effects of vitamin D3 on them remain unknown. The γδ TCR^+T cells respond to phosphor-antigen and act rapidly to infections. They are shown to have pathogenic role in the animal models of autoimmune disorders like EAE and collagen-induced arthritis (CIA). They produce proinflammatory cytokines like IL-17A, IL-17F, *Granulocyte-macrophage colony-stimulating factor*, and IFN-.γ.[66] They express VDR on activation, and in presence of vitamin D3 show inhibition of proliferation and IFN-γ secretion.[67] Currently, it is believed that their main role in autoimmunity is via the secretion of IL-17A.[66] But again, the effect of vitamin D on IL-17A is not known.

The NKT cells recognize glycolipids and give protection against a wide variety of bacteria, viruses, and fungi. Upon TCR activation, they produce inflammatory cytokines including IL-4, IFN-γ, and IL-17A. They have pathogenic role in CIA, but show a protective role in EAE, type I diabetes, and *systemic lupus erythematosus* (SLE).[68] These cells require VDRs in thymus for development and are found hyporesponsive following TCR stimulation in $VDR^{-/-}$mice.[69] The protective effect of $1,25(OH)_2D3$ partially depends on iNKT cells, possibly by inducing IL-4 secretion.

INNATE LYMPHOID CELLS

Recently, a new group of cells called innate lymphoid cells (ILC) have been identified. They are of three: (i) ILC-1 that secretes IFN-γ and depends on T_bet expression; (ii) ILC-2

that secretes group II cytokines-IL-5, IL-13 and depends on GATA 3 expression, and (iii) ILC-3 that secretes IL-17A and/or IL-22 and depends on RORC-RAR related orphan receptor C (RAR-Retenoic acid receptor) expression.

The ILC-1 includes NK cells, which protect against viruses. They have both protective and pathogenic roles in autoimmunity.[70] The $1,25(OH)_2D3$ show variable effects on them, but specifically inhibit their activation, cytotoxicity, and proinflammatory cytokines secretion by the overactive NK cells.[71] The ILC-3s are believed to be pathogenic in autoimmunity. Increased ILC-3s are reported in skin lesion from the psoriasis patients,[72] in intestine in Crohn's disease,[73] In peripheral blood of MS patients,[74] and in the gut, blood, bone marrow, and synovial fluid of joints in ankylosing spondylitis.[75] They have an overall anti-inflammatory effect.

VITAMIN D AND INNATE IMMUNITY

It is already mentioned that vitamin D promotes anti-inflammatory role and enhances the antimicrobial activity. Early evidence of vitamin D as a stimulant of innate immunity indicated its role in the treatment of tuberculosis. More recently, its role was reported of enhanced phagocytic activity of macrophages against the *M. tuberculosis*.[19-21] It was proposed that vitamin D promoted the innate immunity by enhancing the sensing and internalization of *M. tuberculosis* bacteria by macrophages through the TLR2/1 complex.[17] This upregulated expression of both the VDRs and CYP27B1 led to the increased intracrinal $1,25(OH)_2D3$ synthesis, which, on binding to the VDR resulted in killing of pathogens by several mechanisms like transcription of cathelicidin and defensins peptides with antibacterial activity[76,77] and autophagy of the infected cells.[78]

Besides directly fighting infections through antimicrobial agents, vitamin D also influences the innate APCs, especially, the DCs. Different studies have revealed that vitamin D induces a more immature and tolerogenic state in DCs. It also decreases the proinflammatory cytokines secretion[23] and TLRs expression on monocytes.[15] All these changes result in controlling the immune responses and prevention of development of autoimmunity.

The immunoprotective role of vitamin D has also been shown against the commonly encountered airway pathogens in cystic fibrosis.[79] *Helicobacter pylori* in GIT,[78] susceptibility to the viral infections,[80] and in human immunodeficiency virus (HIV) infection. Increased vitamin D deficiency is seen in HIV-infected hosts and in acquired immunodeficiency syndrome patients with very short survival.[81] Laboratory models showed anti-HIV activity by the cathelicidin.[82] Supplementation with vitamin D improved the $CD4^+$ cell counts in HIV-infected patients.[82] However, these results are not equivocal and need further exploration. Genetic susceptibility is also documented.

Low calcitriol levels have been associated with high mortality in severe infections. Such infections usually have high neutrophils. Though these express VDRs, they do not show CYP27B1 expression, resulting in low cathelicidin expression. Calcitriol levels are also reported to be low in such critically ill patients. Hence, a possible role of vitamin D is pointed out in combating such infections by enhancing cathelicidin expression.[83]

VITAMIN D AND ADAPTIVE IMMUNITY

The major effects of calcitriol on key cells involved in adaptive immune response development are already highlighted in detail. It influences DCs, $CD4^+$ T cells, and its subsets, CD8+ T cells as well as B cells.

1,25-Dihydroxy D3 induces the expression of VDRs and vitamin D activating enzymes in T and B cells, more so in their activated and proliferating states.[9] In B cells, calcitriol inhibits their proliferation and differentiation into effector cells as well as secretion of immunoglobulins by them. It also initiates their apoptosis.[27] Initially, calcitriol was thought to mediate these effects through T_H cell subsets; recent findings indicate that it exerts additional direct effects on B cells also, including the development of plasma cells and memory cells.

T cell is also the target of vitamin D3 for immunomodulation.[35] Four major mechanisms of calcitriol influencing T cells proposed are: (1) direct effects due to systemic calcitriol levels; (2) intracrine effects due to the synthesis of calcitriol by the T cells; (3) paracrine effects of the APCs, which also synthesizes calcitriol, and (4) indirect effects due to changes in the APC, which present less antigen. As already said, calcitriol induces the more immature and tolerogenic forms of monocytes during their differentiation and maturation into DCs.

The overall effects of calcitriol can be summarized as follows: (1) It suppresses the cytokines produced by them, (2) it promotes T_H 2 anti-inflammatory cytokine environment by inhibiting proinflammatory cytokines, (3) it inhibits Th17 cell activity including the Th17 cytokines, and (4) it promotes T_{reg} cells development. Taken together, calcitriol supports and regulates adaptive immunity in addition to innate response. Overall, it promotes anti-infective, anti-inflammatory, and tolerogenic immune response.

CONCLUSION

Vitamin D, known earlier for its role in calcium, phosphorus, and skeletal metabolism, has emerged as a key modulator of immune response. It is now clearly known that all cells of the immune system synthesize 1,25 dihydroxy D3

and express VDRs, which make responses to Vitamin D3. Consequently, the significantly high local concentrations of vitamin D3 are achieved, which produce autocrine as well as paracrine functions in addition to well-known endocrine effects. Vitamin D influences the activity of all the major cells involved in immunity. It activates the anti-infective mechanisms of innate immunity and blunts the inflammatory state. Furthern it overall suppresses the adaptive immunity by inhibiting the function of DCs, Th1, Th17 cells, and promoting T_H2 and T_{reg} cells. It also suppresses the B-cell activity including the immunoglobulin secretion. Together, it leads to an anti-infective, anti-inflammatory, and suppressed adaptive immune response state. With increasing understanding of its role in immunity, and widely prevalent vitamin D deficiency, its role is being noticed more in immunological disorders, especially, in autoimmunity and the prevention of infections. Already vitamin D and its analogues are being explored of its therapeutic potential.

FUTURE DIRECTION

The immunomodulatory role of vitamin D3 led to exploration of its possible beneficial role in immune disorders, especially in autoimmune disorders. It was further propelled by the finding that supplementation of $1,25(OH)_2D3$ could prevent the initiation as well as progression of autoimmune diseases in experimental animal models.

Autoimmune disorders represent an abnormal state of immune system in which it fails to discriminate between the self and non-self adequately and consequently, it attacks the innocuous self-antigens resulting in inflammation, tissue damage, and loss of function with widely variable clinical manifestations. More than 100 autoimmune syndromes are known, of which the more common ones are rheumatic arthritis, MS, type I diabetes mellitus (T1DM), Crohn's disease, SLE, irritable bowel syndrome (IBD), etc. These autoimmune diseases affect large populations and the global burden has nearly tripled in the last half century, representing a considerable strain on human and economic resources worldwide. This necessitates the investigation of new avenues for their better management.

In the last few decades, numerous studies have shown a relationship between vitamin D3 and the incidence and severity of autoimmune disease, such as MS, T1DM, and IBD. In view of the weak genetic linkages with low susceptibility, the emphasis has been on finding modifiable environmental factors that act on susceptible genotype to produce disease phenotypes. The key questions being explored are: (i) what are the dominant environmental stressors, (ii) by what mechanisms do they act, and (iii) if they can lead to an etiology-based preventive and therapeutic strategies. Vitamin D appears to be promising, but needs to be further explored before its therapeutic use is established.

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