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REVIEW

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The interplay between vitamin D and viral infections

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Summary

The pleiotropic role of vitamin D has been explored over the past decades and there is compelling evidence for an epidemiological association between poor vitamin D status and a variety of diseases. While the potential anti-viral effect of vitamin D has recently been described, the underlying mechanisms by which vitamin D deficiency could contribute to viral disease development remain poorly understood. The possible interactions between viral infections and vitamin D appear to be more complex than previously thought. Recent findings indicate a complex interplay between viral infections and vitamin D, including the induction of anti-viral state, functional immunoregulatory features, interaction with cellular and viral factors, induction of autophagy and apoptosis, and genetic and epigenetic alterations. While crosstalk between vitamin D and intracellular signalling pathways may provide an essential modulatory effect on viral gene transcription, the immunomodulatory effect of vitamin D on viral infections appears to be transient. The interplay between viral infections and vitamin D remains an intriguing concept, and the global imprint that vitamin D can have on the immune signature in the context of viral infections is an area of growing interest.

KEYWORDS

immune response, viral infection, Vitamin D

1 | INTRODUCTION

Vitamin D difficiency is recognized as a global public health problem. Indeed, several epidemiologic studies indicate that poor vitamin D status can have an impact on a range of diseases.[1-5]

Skin is the main natural source of vitamin D synthesis. As illustrated in Figure 1, exposure to ultraviolet (UV) rays from sunlight and heat convert 7-dehydrocholesterol (7-DHC) to previtamin D3 and vitamin D3, respectively. Vitamin D3 then localizes to the liver using vitamin D-binding protein (VDBP). In the liver, vitamin D is first converted to 25 hydroxyvitamin D [25(OH)D] using cytochrome P450 family 2 subfamily R member 1 (CYP2R1).[6,7] 25(OH) D then transported to the kidneys where it is converted to the active form, 1,25 dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol, using cytochrome P450 family 27 subfamily B member 1 (CYP27B1). 1,25(OH)2D is finally converted to 24,25(OH)2D by cytochrome P450 family 24 subfamily A member 1 (CYP24A1). Vitamin D exerts its regulatory effects when the active form binds to its cognate nuclear vitamin D receptor (VDR). Upon interaction with its ligand, VDR heterodimerizes with the retinoic X receptor (RXR) and then binds to

Abbreviations: 1,25(OH)2D, 1,25 di-hydroxy-vitamin D; 25(OH)D, 25 hydroxyvitamin D; 7-DHC, 7-dihydrocholesterol; CAMP, Cathelicidin antimicrobial peptide; CHDPs, Cationic host defence peptides; CXCR4, C-X-C chemokine receptor type 4; CYP24A1, cytochrome P450 family 24 subfamily A member 1; CYP27B1, cytochrome P450 family 27 subfamily B member 1; CYP2R1, cytochrome P450 family 2 subfamily R member 1; DCs, Dendritic cells; EBNA1, EBV nuclear antigen 1; EGFR, Epidermal growth factor receptor; FPRL1, Formyl peptide receptor–like 1; HAART, Highly active antiretroviral therapy; HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HATs, Histone acetyl transferases; HBDs, Human β-defensins; HCEC, Human corneal epithelial cells; HDACs, Histone deacetylases; HESN, HIV-1-exposed but seronegative; HPV, Human papillomavirus; IE, Immediate early; ISGs, Interferon stimulated genes; MS, Multiple sclerosis; MxA, Myxovirus resistance protein 1; pSTAT-1, Phosphorylated STAT-1; RV, Rhinovirus; RXR, Retinoic X receptor; SNP, Single nucleotide polymorphisms; SRC-1, Steroid receptor coactivator 1; SRs, Scavenger receptors; SVR, Sustained virological response; TGF-β, Transforming growth factor-β; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TLR, Toll-like receptor; Tregs, Regulatory T cells; UV, Ultraviolet; VDBP, Vitamin D-binding protein; VDR, Vitamin D receptor; VDRE, Vitamin D responsive elements; vGPCR, Viral G protein-coupled receptor associated to Kaposi sarcoma

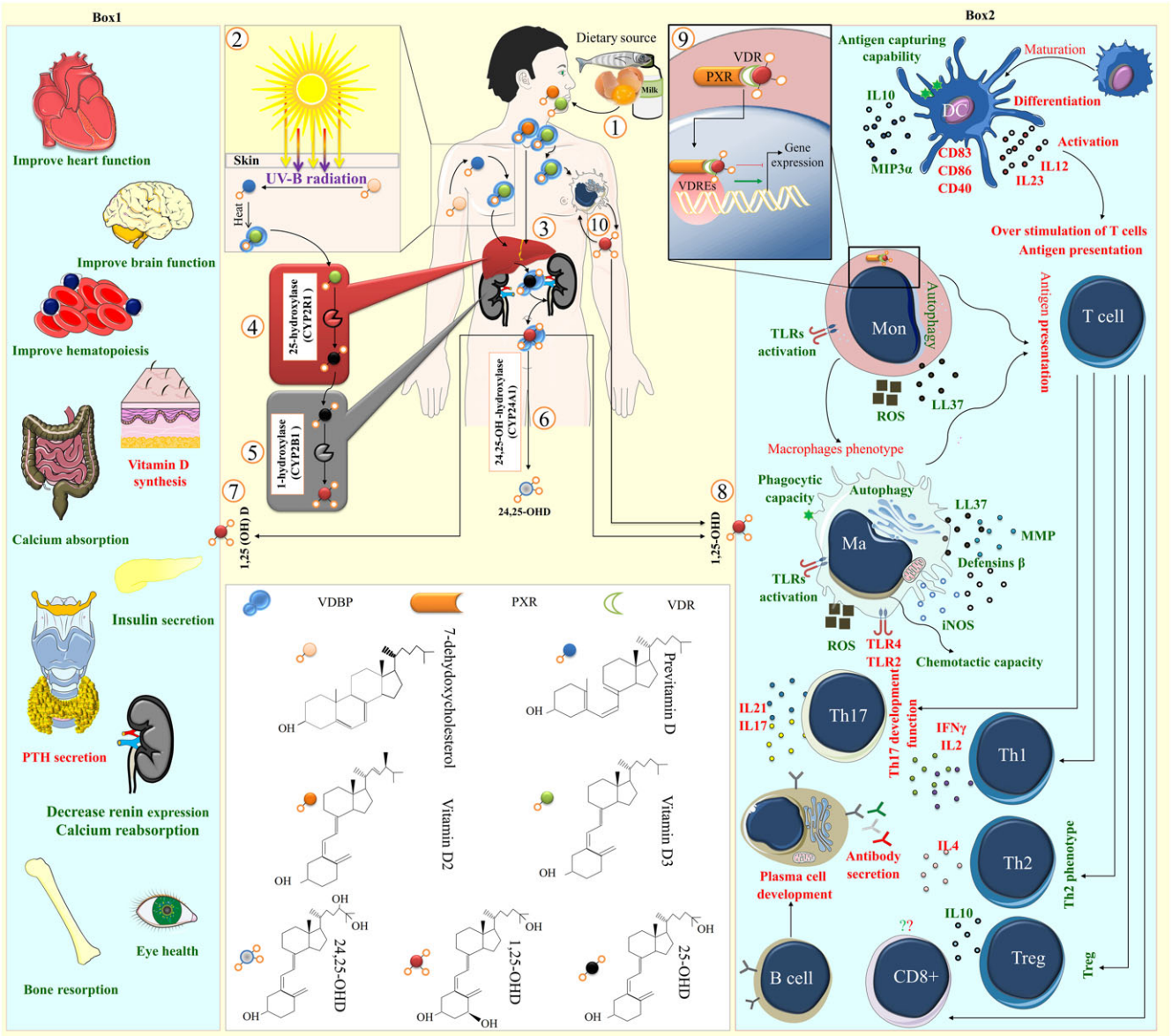

FIGURE 1 The metabolism of vitamin D and its effect on nonimmune and immune cells. (1) Vitamin D is obtained primarily from food, (2) nevertheless sunlight exposure in the skin, where the UV rays alter 7-DHC to pre-vitamin D3, which is the main source of vitamin D3. Pre-vitamin D3 finally is converted into vitamin D3 by heat. (3) all obtained vitamin D is localized to the liver via VDBP. (4) in the liver, 25-hydroxylase converts vitamin D to 25(OH)D. (5) 25(OH) D is transported to kidneys for conversion to 1,25(OH)2D by the action of CYP27B1. (6) 1,25(OH)2D is inactivated and converted to 24,25(OH)2D by CYP24A1. (7) 1,25(OH)2D binds to VDR on target cells. VDR is expressed in various cell jargons such as intestine, bone, kidneys, skin, parathyroid, heart, muscle, eyes, brain, pancreatic beta-cells, and epithelial cells, and also (8) cells of the immune system. (9) on one hand, vitamin D alters some metabolic functions and tissue function (box 1); on the other hand, binding of the metabolites of vitamin D to VDR leads to VDR and RXR heterodimer formation. Consequently, binding of this dimer-to-promoter region of VDREs induces and/or represses transcription of many genes. Expression of VDRs in almost all immune cells indicates that these are one of the main target of vitamin D, and numerous immune biomarkers are modulated via VDRs action (box 2). (10) given the fact that immune cells also express CYP27B1, it can locally facilitate the conversion of 25(OH) D to 1,25(OH)2D. Green color: Induction or increase of expression by vitamin D. red color: Inhibition or decreases of expression by vitamin D. abbreviation: 7-DHC, 7-dihydrocholesterol (7-DHC); 1,25 di-hydroxy-vitamin D [1,25(OH)2D], 25 hydroxy-vitamin D [25(OH)D], cytochrome P450 family 27 subfamily B member 1 (CYP27B1), cytochrome P450 family 24 subfamily a member 1 (CYP24A1), cytochrome P450 family 2 subfamily R member 1 (CYP2R1), retinoic X receptor (RXR), toll-like receptor (TLR), vitamin D receptor (VDR), vitamin D responsive elements (VDRE)

vitamin D–responsive elements (VDREs) in the promoter region of target genes.[7,8]

While there is compelling evidence in favour of an epidemiological association between vitamin D deficiency and a range of diseases (Table 1), the underlying mechanisms by which poor vitamin D status may contribute to disease development and, in particular, viral infections is still in its infancy. The plausible interactions between viral infections and vitamin D appears to be more complex than previously thought. Several mechanisms have been suggested to be involved in this regard. For the purpose of this review, we mainly focus on more general mechanisms including: (1) induction of antimicrobial peptides, (2) immunoregulatory function, (3) interaction with key cellular and

TABLE 1 The correlative studies showing a positive or negative association between vitamin D level and viral infections

Virus	Correlation	Clinical marker	25(oh)D	1,25(oh)2D	Clinical condition	Reference
EBV	Negative	Positive monospot test	+	−	Infectious mononucleosis	Maloney et al[9]
		EBV load	+	−	Multiple sclerosis	Nejati et al[10]
		Anti-EBNA-1 antibody levels	+	−	Multiple sclerosis	Rolf et al[11]
	Positive	EBNA-1 IgG antibody	+	−	Multiple sclerosis vs control group	Mowry et al[12]
VZV	Positive	VZV-IgG levels	+	−	Chronic dialysis patients	Chao el al[13]
CMV	Positive	CMV-IgG level	+	−	Multiple sclerosis vs control group	Mowry et al[12]
Influenza	Positive	HA inhibition assay titers and influenza-specific granzyme-B response	+	−	Prostate cancer	Chadha et al[14]
RSV	Negative	RSV lower respiratory tract infection in the first year of life	+	−	Neonates (cord blood plasma)	Belderbos et al[1]
		Risk of the need for intensive care unit admission and invasive mechanical ventilation	+	−	Lower respiratory tract infection with RSV and/or human metapneumovirus	Hurwitz et al[15]
HIV	Negative	HIV infection and viral load	+	−	Perinatally HIV-infected	Rutstein et al[16]
		Mortality	+	−	HIV-infected adults undergoing antiretroviral therapy	Sudfeld et al[17]
		Preterm birth, anemia, hypochromic microcytosis, viral load, and hepatitis B infection	+	−	HIV-infected pregnant women	Hidron et al and Jao et al[18,19]
		Severe diseases (diabetes, cardiovascular, renal), AIDS, death, and CD4 count	+	−	HIV-positive naïve	Vescini et al[20]
		HIV disease progression, mortality, and anemia	+	−	HIV-infected women	Mehta et al[21]
		Subclinical arterial dysfunction	+	−	HIV-cardiovascular patients	Shikuma et al[22]
		Type II diabetes mellitus, silent coronary artery disease, oral candidiasis and calprotectinemia, co-infection with HCV, detectable HIV viremia, serum IL-6, mortality, AIDS events, and HIV RNA	+	−	HIV-positive	Viard et al, Yancheva et al, Adeyemi et al, Szep et al, Lai et al, and Sroussi et al[23-28]
		Plasma HIV RNA	+	−	AIDS/Kaposi sarcoma	Erlandson et al[29]
		HIV infection	+	−	Veterans with and without HIV	Hidron et al[18]
		Mother-to-child transmission and breast-feeding mother-to-child transmission	+	−	HIV-infected pregnant women (maternal serum)	Mehta et al[30]
		HIV RNA	+	−	HIV-positive injection drug users	Lambert et al[31]
		TNF-α level	−	+	HIV-positive	Haug et al[32]
		HIV infected	+	−	HIV-infected and uninfected women	Adeyemi et al[25]
	Positive	Poorer immune status	+	−	Perinatally acquired HIV	Rutstein et al[16]
		HIV infection	+	−	HIV-infected vs uninfected injection drug users	Lambert et al[31]
		Serum IL-10, IFN-γ, TNF-α, advanced liver disease, HCV infection and CD4 T-cell count recovery	+	−	HIV-positive patients	Hidron et al and Yancheva et al[18,24]
		CD4 count	+	−	HIV-infected postmenopausal women	Stein et al[33]
		CD4+ cell count and HCV antibody seropositive	+	−	HIV-infected injection drug users	Lamber et al[31]
		Viral load	+	−	HIV-positive naïve	Vescini et al[20]
		Viral load, CD4 count	−	+	HIV-infected	Adeyemi et al and Haug et al[25,32]
		Virologic response to PEG IFN + RBV	+	−	HIV-HCV coinfected patients	Mandorfer et al[34]
HCV	Negative	Severity and progression of liver fibrosis (Metaanalysis)	+	−	Chronic hepatitis C patients	Dadabhai et al[35]
		Persistent infection	+	−	Hepatitis C patients	Wu et al[36]
		Severe fibrosis	+	−	Chronic hepatitis C genotype 1 patients	Petta et al[37]
	Positive	Sustained virological response (Metaanalysis)	+	−	Hepatitis C virus infection	Villar et al[38]

(Continues)

TABLE 1 (Continued)

Virus	Correlation	Clinical marker	25(oh)D	1,25(oh)2D	Clinical condition	Reference
HBV	Negative	DNA viral load	+	−	Chronic hepatitis B	Farnik et al[39]
		HBV-DNA load and progression to liver cirrhosis	+	−	HBV patients	Hoan et al[40]
		Hepatitis B-related cirrhotic patients	+	−	Chronic hepatitis B patients	Zhao et al[41]
		(HBeAg)-positivity	+	−	Chronic hepatitis B patients	Farnik et al[39]
	Positive	Spontaneous HBsAg seroclearance	+	−	Chronic-inactive hepatitis B	Muhamid et al and Yu et al[42,43]
HPV	Negative	Cervicovaginal human papillomavirus infection	+	−	Sexually-active women	Jung et al[44]

viral factors, (4) induction of autophagy and apoptosis, (5) epigenetic elements, and (6) genetic polymorphisms.

1.1 | Induction of antimicrobial peptides

Cationic host defence peptides (CHDPs), also known as antimicrobial peptides, play an important role in the innate immune defense against intracellular pathogens. Antimicrobial peptides such as cathelicidins not only exert direct microbicidal effects but also show pleiotropic properties such as inducing immune modulatory responses to pathogen-associated stimuli.[45]

Studies of innate immunity have shown that intracrine induction of antimicrobial activity by vitamin D is a pivotal component of monocyte/macrophage response to infection.[46] Antimicrobial activity of vitamin D is mainly dependent on the induction of the cathelicidin antimicrobial peptide.[47] Human cathelicidin peptide LL37 exhibits antimicrobial activity through interacting with formyl peptide receptor–like 1 (FPRL1) and by recruiting neutrophils, monocytes, and T cells to microbial invasion sites (Figure 2).[48] LL37 may also contribute to innate immunity by transactivating the epidermal growth

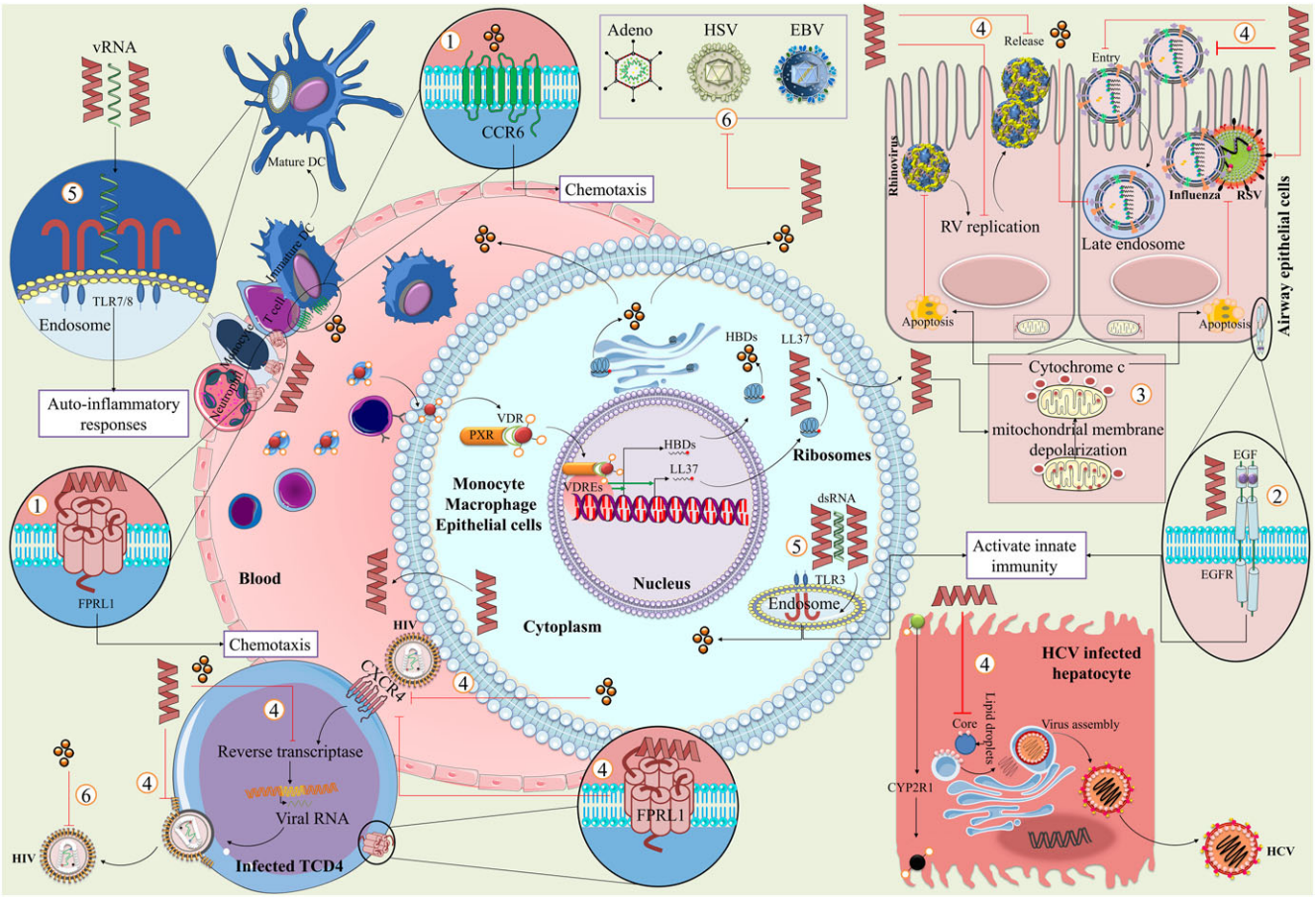

FIGURE 2 Vitamin D and induction of antimicrobial peptides against viral infection. Vitamin D-induced antimicrobial peptides (LL37 and HBDs) via VDR and RXR dimerization act against viral infections through (1) binding to FPRL1 and CCR6 for recruiting immune cells to site of infection; (2) activation of innate immunity by transactivation of the EGFR; (3) clearance of viral infection through mitochondrial membrane depolarization and release of cytochrome c; (4) down-regulation of cell entry, replication, and viral release; (5) protection of viral RNAs from degradation and induced immunity response through TLRs activation; (6) and direct effects on virions. Abbreviation: Epidermal growth factor receptor (EGFR), formyl peptide receptor–like 1 (FPRL1), human β-defensins (HBDs), retinoic X receptor (RXR), toll-like receptor (TLR), and vitamin D receptor (VDR)

factor receptor (EGFR) at the airway epithelial surface.[49] Furthermore, LL37 can promote the clearance of respiratory pathogens by inducing apoptosis of infected epithelial cells through enhanced mitochondrial membrane depolarization and release of cytochrome *c*.[50]

The potential anti-viral effect of such antimicrobial peptides has recently gained attention in the field of virology. Indeed, the potent anti-viral activity of cathelicidin was demonstrated against several viral infections including HIV-1,[51] vaccinia virus,[52] HSV-1/2,[53,54] influenza,[55] rhinovirus (RV),[56,57] and HCV.[58,59]

LL37 inhibits viral infection by blocking either viral entry into host cells or suppressing virus activity. Indeed, in vitro exposure of influenza viruses (H1N1 and H3N2) to LL37 peptide was found to significantly decrease the infection's titre. The anti-viral activity of LL37 against influenza viruses is partially mediated by a direct effect on the virion without affecting HA function or altering viral uptake.[60] Although yet to be fully defined, the mechanisms by which LL37 modulate inflammation in viral infections may relate to the modulation of Toll-like receptor (TLR) signalling.[61] It has been recently shown that LL37 can mediate the inflammatory activity by a cell-surface-dependent interaction rather than directly enhancing membrane permeability. Indeed, LL37 promoted the recognition of nucleic acids in human cells by facilitating dsRNA binding to cell surface scavenger receptors (SRs), which then results in endocytosis to trigger inflammatory activation.[62]

LL37 was also found to enhance the recognition of viral dsRNA by TLR3. Although viral dsRNAs can activate TLR3 during viral infection, the level of activation is generally low and additional co-factors may be needed to increase the ability of TLR3 to recognize viral dsRNAs. It is likely that LL37 modulates TLR3 signalling rather than activating TLR3 gene expression. LL37 also facilitates dsRNAs trafficking to enhance TLR3 signalling.[63] LL37 binds and protects self-RNA from enzymatic degradation by transporting self-RNAs into endocytic compartments of dentritic cells (DCs). Self-RNA-LL37 complexes can induce auto-inflammatory responses through activating TLR7 and TLR8 in human DCs.[64]

It has been shown that virus envelope proteins of HIV-1 (gp41 and gp120) contain FPR-recognizing peptide sequences.[65] Given the fact that LL37 can act as agonist for formyl peptide receptors (FPRs), this may explain its inhibitory effect on HIV-1 replication in PBMCs. However, the inhibitory effect of LL37 on various HIV isolates appears to be less dependent of FPRL-1 signalling with no detectable changes in the expression of HIV-1 chemokine receptors.[51] Moreover, LL37 was shown to inhibit HIV-1 reverse transcriptase activity in a dose-dependent manner that was independent of any changes in expression of virus receptors.[66]

The potent anti-viral activity of LL37 against HSV-1 has also been reported in human corneal epithelial cells (HCECs) and appears to be mainly because of the blocking of virus binding to the cells as the peptide was ineffective once HSV-1 was internalized.[67] The anti-viral effect of LL37 was also reported in a HCV cell culture system. Indeed, pretreatment of Huh-7 cells with different concentrations of LL37 (2-20 μg/mL) attenuated HCV infection approximately 2 to 10-fold as shown by decreased intra- and extracellular levels of HCV core antigen. Supplementation with vitamin D is thought to induce elevated levels of LL37, which might improve the efficacy of treatment when used in combination with IFN-based therapy.[68] However, further studies are required to confirm if LL37 exerts its anti-viral effect independently or in combination with other intrinsic defense factors.

Vitamin D also induces the production of human β-defensins (HBDs),[69] which can facilitate the anti-viral state against viral infections. As illustrated in Figure 2, vitamin D exerts its potential anti-viral effects through direct and/or indirect mechanisms. While HBDs indirectly modulate the immune cells migration to the site of infection, they may exert direct anti-viral effects through viral membrane interruption, interference with viral glycoproteins, constraints on the virus replication, and down regulation of virus receptors,[64] as reported on viruses such as HIV-1,[70,71] vaccinia,[52] adenovirus,[72] RV,[73] and influenza virus.[74]

Potential involvement of vitamin D has also been suggested with regards to the natural resistance to HIV-1 by showing higher mRNA levels of cathelicidin and TLR4 in oral-mucosa and PBMCs, along with higher CYP24A1 mRNA in vaginal-mucosa in HIV-1-exposed but seronegative individuals (HESNs) compared with nonexposed controls.[75]

Although the precise mechanisms by which vitamin D induces antimicrobial peptides have yet to be defined, the anti-viral effects appear to be broad and vary in a cell type and virus-specific manner.

1.2 | Immunoregulatory function

The immunomodulatory functions of vitamin D have received much attention. Besides its classical role in bone and calcium homeostasis, vitamin D is a potent immune regulator[76] in different settings as described in Figure 1, box 2. Vitamin D is thought to modulate the immune responses by selective suppression of effector functions such as inflammatory cytokine production and leukocyte infiltration into inflammatory sites, which may minimise inflammation.[77-79] Vitamin D deficiency was also shown to be associated with an increased CD4/CD8 ratio.[80] If this is the case, poor vitamin D status may reduce the ability of the immune system to produce activated T lymphocytes such as CD8+ T cells that can attack virally infected B cells, and impair the control of viral infections such as EBV.[81] Given the important role of vitamin D in T cell regulation, serum levels of vitamin D have been shown to be associated with the suppressive function of regulatory T cells (Tregs).[82] Moreover, a positive correlation between vitamin D level and influenza-specific granzyme B cellular responses has been reported.[14]

A potential role for vitamin D in B-lymphocyte-related disorders has also been highlighted by showing that 1,25(OH)2D can inhibit the differentiation of B-lymphocytes to plasma cells and class-switched memory B-cells.[83] The inhibitory effect of vitamin D appears to be through the action of IL10-producing regulatory lymphocytes. Indeed, it has been suggested that a defect in IL10 could abrogate the anti-inflammatory functions of vitamin D.[84] Given the important role of IL10-producing regulatory lymphocytes, production of viral IL10 during EBV infection may also diminish the protective effects of vitamin D in patients with multiple sclerosis (MS).[85]

The immunomodulatory effect of vitamin D on viral infections appears to be transient. In support of this observation, reduced levels of antibodies against EBV nuclear antigen (EBNA)-1 has been found following 48 weeks of high-dose oral vitamin D3 supplementation in

MS patients. However, this reduction was not observed after 96 weeks, suggesting that high-dose oral vitamin D3 supplementation may only lead to a transient increase in the amount of 1,25 (OH)2D available in immune cells.[86]

Viral infections may further up-regulate CYP27B1 by converting more circulating vitamin D to its active form and therefore synergize with vitamin D to induce cathelicidin at the site of infection or injury.[87] Respiratory epithelial cells constitutively express CYP27B1, and local activation of vitamin D within these cells is thought to exert important immunomodulatory effects. High level expression of activating CYP27B1 in primary lung epithelial cells can increase the expression of vitamin D-regulated genes, particularly those with important immunomodulatory functions.[88] This process appears to have a beneficial impact in response to viral infections, particularly respiratory viruses. Indeed, exposing airway epithelium to vitamin D was shown to induce NF-kB-linked chemokines and cytokines with a potential beneficial effect on host defense against RSV without jeopardizing viral clearance.[88] It appears that vitamin D influences acute lower respiratory tract infections through reducing inflammation. This can be important particularly in young children who suffer from both severe acute lower respiratory infection and poor vitamin D status.[2]

The level of vitamin D was also shown to be negatively correlated with HBV-DNA levels in patients with chronic hepatitis B, suggesting that deficient vitamin D status may be related to the development of increased viral replication and reduced HBV-mediated immune responses.[89] Given the fact that vitamin D deficiency can contribute to the inflammatory process and oxidative stress imbalance in patients with HCV, it may lead to changes in particular intracellular signalling pathways that are involved in liver injury and enhanced inflammation.[90] Poor vitamin D status may also impair the recovery of CD4+ T cells in HIV-infected patients with advanced disease on highly active antiretroviral therapy (HAART). While the average number of CD4+ T cells in patients with insufficient vitamin D levels was found to be significantly lower over time when compared with patients with sufficient levels,[91] supplementation of vitamin D even at high dosage (1600 IU/day) failed to impact on CD4 count in HIV-infected children.[92]

Given the chronic inflammatory state of HIV infection, insufficient local production of vitamin D, together with virus infection may worsen the ongoing chronic inflammation associated with infection.[93] A beneficial effect on both health and survival outcomes has been reported in HIV-infected patients following daily supplementation with multivitamins (with a median follow-up of 71 months), which is thought to be mediated through enhancing T cell counts and reducing viral loads.[94,95] The reported regulatory effects of vitamin D on human monocyte HLA-DR and CD4 antigen expression[96] may facilitate the host system resistance to viral entry. Pre-treatment of freshly isolated human peripheral blood monocytes with 1,25(OH)2D3 was reported to reduce productive infection with HIV.[97] Although the exact mechanism has not been defined, vitamin D was shown to increase the mRNA expression of T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) that is thought to block the release of HIV-1-.[98]Although a beneficial role of vitamin D in immune function may explain its protective effect against HIV disease progression, an enhanced productive HIV infection has also been reported by vitamin D compounds.[99] For example, it was shown that vitamin D increase the expression of C-X-C chemokine receptor type 4 (CXCR4) on HIV target cells, which may provide a more permissive state leading to enhanced viral replication.[100] These contradictory observations may suggest a dual role for vitamin D. While a beneficial role is suggested during acute phase of HIV-1 infection, it might be detrimental during the chronic phase of HIV-1 infection.[71]

Toll-like receptors are key components in pathogen recognition and crucial mediators in the early inflammatory response to viral infections. Down-regulation of TLRs by vitamin D and its metabolites has been suggested as another important immunomodulatory effect. Stimulation of human macrophage with TLR1/2 heterodimers was found to induce expression of CYP27B1 and VDR. This may lead to the induction of antimicrobial peptides and contribute to microbial infection susceptibility.[101] The mechanisms by which vitamin D and dsRNA synergize to alter gene expression is not known. However, it appears that the interplay between VDR and other activated transcription factors may play an important role against viral infection. Differential responsiveness of TLRs was also observed following the stimulation of PBMCs or CD14+ monocytes with TLR4 and TLR7/8 selective ligands in the presence of 1,25(OH)2D. While stimulation with TLR4 ligand showed around 50% inhibition of immune responses (both pro-inflammatory and anti-inflammatory), stimulation with TLR7/8 ligands failed to induce innate immune responses in the presence of vitamin D. This differential responsiveness was attributed to the inhibition of VDR mRNA and protein expression by TLR7/8, but not TLR4.[102] Although the detailed mechanisms are yet to be defined, TLR8 agonists have been suggested to inhibit HIV replication in macrophages through a cathelicidin antimicrobial peptide (CAMP)-dependent autophagic response.[103] Pre-exposure of HSV-1-infected Hela cells with vitamin D was also shown to influence viral immunopathogenesis via downregulation of TLR2 and 9.[104] Given the role of TLRs in viral pathogenesis, supplementation of vitamin D may be beneficial.

Downregulation of inflammatory cytokines is another mechanism by which vitamin D may play a role in viral infections. Vitamin D was reported to inhibit HIV transcription from latently infected cells by reducing TNF-α-driven transcription.[105] It has also been shown that exposure of influenza-infected human lung epithelial cells to vitamin D can significantly decrease the levels of inflammatory cytokines or chemokines such as TNF-α, IFN-β, IL8, IL6, and RANTES.[106]Moreover, vitamin D treatment of RSV-infected human airway epithelial cells can decrease the mRNA expression levels of IFN-β, myxovirus resistance protein 1 (MxA), and interferon-stimulated genes (ISGs).[88] In addition to its anti-inflammatory function, vitamin D could enhance secretion of pro-inflammatory chemokines (CXCL8 and CXCL10), which may modify the anti-viral response.[107] Vitamin D treatment of primary monocytes and a monocytic cell line was shown to induce the lytic phase of CMV replication and is thought to be associated with the monocyte maturation/differentiation state.[108]

The immunomodulatory role of vitamin D in viral infections is more complex and appears to vary based on the nature of pathogen and the type of immune function that is primarily responsible for disease resolution.[109,110] In addition, the anti-viral effects of vitamin D appears to be transient, ranging from differentially regulated viral immune responses to regulation of viral pathogenesis either directly or indirectly (Figure 3).

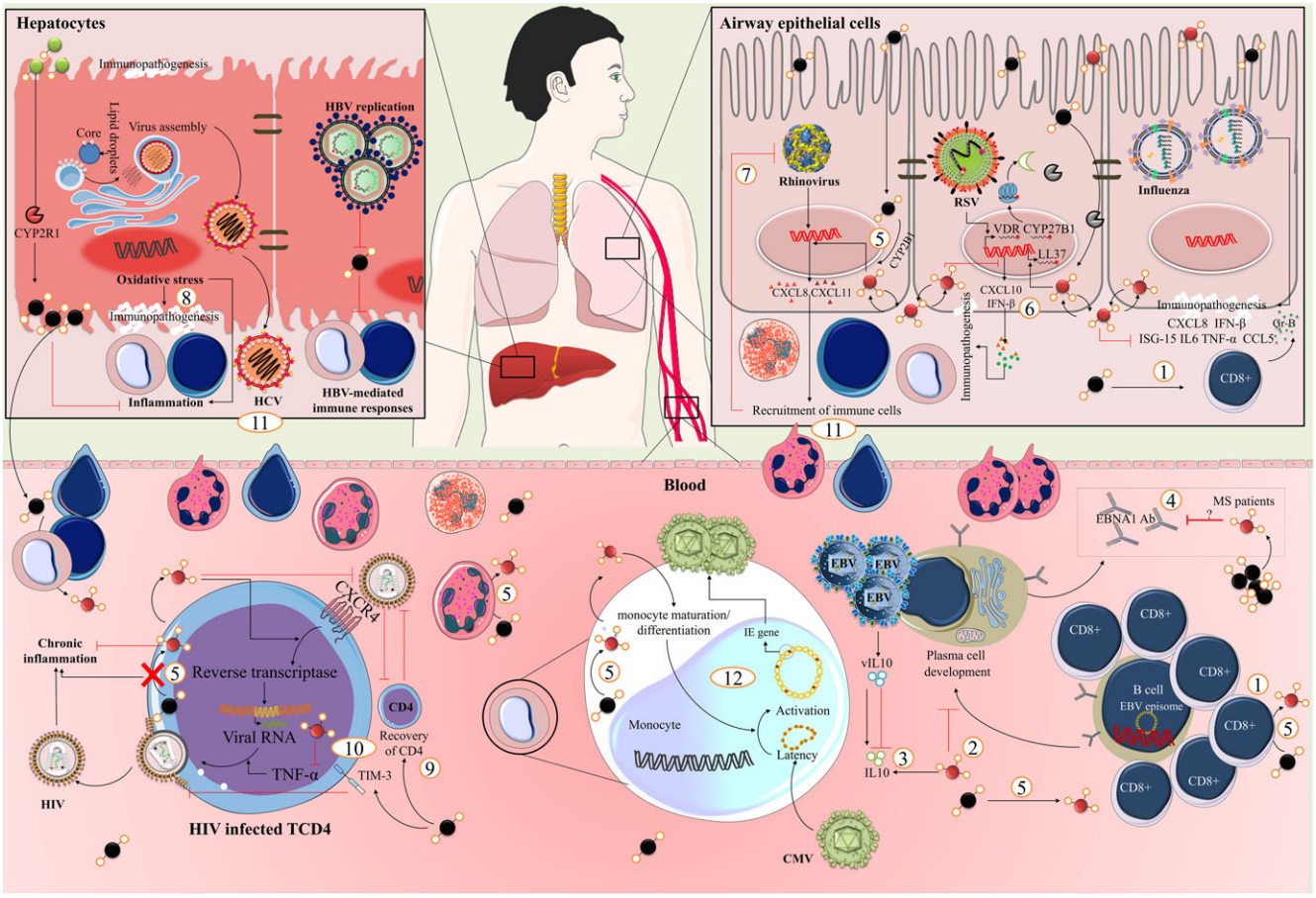

FIGURE 3 Vitamin D and immunoregulatory function. The immunoregulatory functions of vitamin D in viral infections include: (1) increasing virus specific CD8+ T cells (EBV and influenza), (2) inhibition of B cell differentiation to plasma cells and class-switched memory B cells (EBV), (3) compromising the function of IL10-producing regulatory cells (EBV), (4) reduced levels of antibody against viruses available in immune cells (Epstein–Barr nuclear antigen (EBNA)-1), (5) inducing cathelicidin at the site of infection or injury, and therefore synergizing with vitamin D through up-regulation of CYP27B1 by local conversion of more circulating vitamin D to its active form (respiratory viruses), (6) induction of CXCL10 and IFN-β in airway epithelium (RSV), (7) decreased viral replication (HBV and rhinovirus), (8) imbalancing inflammatory process and oxidative stress (HCV), (9) recovery of CD4+ T cells (HIV), (10) facilitating host resistance against viral entry and viral replication (HIV), (11) recruitment of immune cells to the site of infection (respiratory and hepatitis viruses), and (12) alteration of infection phase in latently infected cells (HIV and CMV). Abbreviation: Cytochrome P450 family 27 subfamily B member 1(CYP27B1), IFN-stimulated gene-15 (ISG15), granzyme B (gr-B), vitamin D receptor (VDR)

1.3 | Interaction with key cellular and viral factors

Given the fact that the vitamin D receptor shares a common structure in terms of functional domains and homologies with other transcription factors in the superfamily of nuclear receptors, interaction with specific regulatory factors is another mechanism by which vitamin D may control transcription of target genes. VDR can physically interact with some regulatory proteins in order to regulate gene expression through binding to specific DNA response elements in the promoter region of target genes.[111] Studies performed on mammalian cells have shown that SMAD3 can act as a specific coactivator for ligand-induced transactivation of VDR. Since Smad family members are considered as the essential intracellular signalling components of the transforming growth factor-β (TGF-β) superfamily, Smad3 has been suggested to play a role in cross-talk between vitamin D and TGF-β signalling pathways.[112] Furthermore, the inhibitory effect of TNF-α on the transcriptional potency of vitamin D was shown to be mediated by p65 as a NF-κB subunit.[113] Upon stable integration of the p65 subunit into the VDR transcription complex, p65 can reduce the efficiency of transcription through disrupting VDR binding to steroid receptor coactivator 1 (SRC-1).[114] As shown in macrophages and endothelial cells transformed by the KSHV viral G protein-coupled receptor (vGPCR), vitamin D can also exert its growth inhibitory effects by decreasing NF-κB translocation to the nucleus and increasing the expression of IκBα protein.[115] Furthermore, vitamin D is reported to negatively regulate IL12 production via downregulating the NF-kB activation and binding to the p40-kB sequence.[116] The interplay between VDR and viral proteins or cellular transcription factors highlights the role that vitamin D plays in viral infections.

A potential physiological interaction between viral infection and vitamin D has been reported in EBV infection through the blocking effect of EBNA3 on the transcription of VDR responsive genes[117,118] and the observation that EBNA2 and VDR that may interact with each other inside DNA binding sites. A remarkable overlap between EBNA2 and VDR binding sites with MS-susceptibility regions further

highlight the role of these environmental factors in MS disease. While it was shown that EBNA2 drives the proliferation of B-lymphocytes and their survival in primary infection,[119] vitamin D plays a prominent role in the maintenance of B-cell homeostasis through preferential down regulation of B-cell function.[120]

Vitamin D is thought to exert its potential role in reducing immunopathology of RSV infection by dampening the inflammatory response through increasing IκBα levels. RSV infection of pre-treated alveolar A549 cells with 1,25(OH)2D was shown to decrease phosphorylated STAT-1 (pSTAT-1) levels and increase IκBα protein levels, preventing its translocation into the nucleus and subsequent binding to DNA promoter regions.[121]

VDR may also play an important role in liver responses to chronic damage induced by viral infection. VDR has been widely detected in the liver and the expression of CYP2R1 in hepatocytes correlated strongly with VDR positivity on liver inflammatory cells. Low hepatic VDR expression was found to be associated with more severe liver histology, which may represent the primary event leading to the progression of hepatitis. It may also represent a consequence of the underlying liver disease that impairs cellular metabolism and protein synthesis/expression.[122] The stimulatory effect of VDR on HIV-1 LTR transactivation has also been reported using in vitro studies showing that VDR can activate the long terminal repeat of HIV-1 in a ligand-dependent manner through nonclassical nuclear receptor transcriptional actions, which might ensure viral transcription under different physiological scenarios.[123] Increased utilization by T lymphocytes and the effects of antiretroviral treatments on the metabolic pathways of vitamin D may justify the lower concentration of vitamin D during HIV infection.[124] It has been shown that vitamin D acts as a negative endocrine regulator of renin,[125,126] which may have

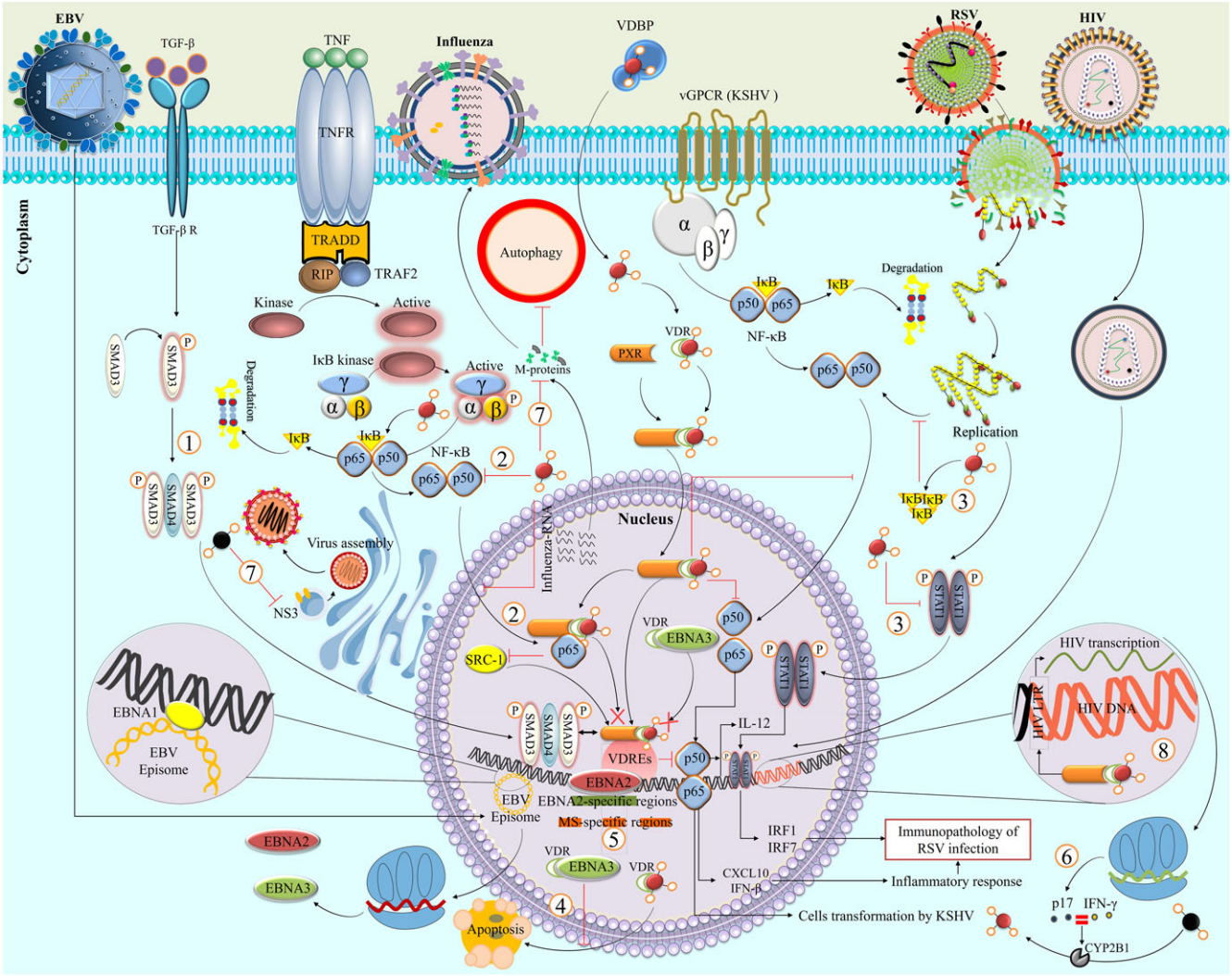

FIGURE 4 Vitamin D interaction with cellular and viral factors. Interaction between certain regulatory factors is a potential mechanism for the influence of vitamin D on virus infections such as (1) acting as a coactivator specific for ligand-induced transactivation of VDR that cross-talk between vitamin D and TGF-β signaling pathways (many viruses-Smad3), (2) inhibitory effect via integrating into the vitamin D-stimulated nuclear protein complex (many viruses-NF-κB subunits and TNF-α), (3) inhibition of vitamin D induced apoptosis (EBV-EBNA3), (4) overlapping with VDR binding sites (EBV-EBNA2), (5) vitamin D reduced immunopathology of viral infections, probably by inducing the inflammatory inhibitors (RSV-IκBα) and preventing its translocation into the nucleus and subsequent binding to DNA promoter regions (RSV-NF-κB, IL-12,IRF1, IRF7, and pSTAT-1), (6) inducing CYP27B1 activity (HIV p17 matrix protein), (7) vitamin D decreased viral proteins (influenza M and HCV NS3 proteins), (8) and activated of viral replication (HIV-1 LTR). Abbreviation: Phosphorylated STAT-1 (pSTAT-1), retinoic X receptor (RXR), steroid receptor coactivator 1 (SRC-1), vitamin D receptor (VDR), viral G protein-coupled receptor associated to Kaposi sarcoma (vGPCR)

important implications in viral infections. The suppression of VDR in T cells was found to be associated with increased levels of renin and Angiotensin II. The interaction of renin with HIV gag in T cells was reported to be associated with enhanced HIV-1 replication.[127]

Given the fact that apolipoprotein A1 and C3 also play an important role in infectious virus production of HCV, treatment with 25(OH) D3 was recently shown to suppress the expression of these apolipoproteins.[128] Moreover, vitamin D may selectively inhibit the virus assembly by interference with NS3[59] and so Vitamin D may be an addition to HCV anti-viral drug therapy regimens.

Figure 4 illustrates the relationship between vitamin D and cellular and viral factors in the context of infection outcomes.

1.4 | Induction of autophagy and apoptosis

Autophagy and apoptosis can impact several aspects of innate and adaptive immunity through a distinct set of adaptors leading to enhanced host resistance against microbial insults.[129] As illustrated in Figure 5, the induction of autophagy and apoptosis is another mechanism by which vitamin D may exert its potential effects. Vitamin D signalling pathways that alter autophagy appear to be different from those affecting calcium signalling and may depend on the type of organism and cell-specific conditions.[130] At least two overlapping pathways appear to be involved in the induction of autophagy by vitamin D. Firstly, binding of vitamin D to VDR promotes the formation of the PI3KC3 kinase complex, which leads to autophagosome elongation and subsequent fusion of the autophagosome with a lysosome.[131] Secondly, binding of Vitamin D to its receptor upregulates the antimicrobial peptide cathelicidin, which can lead to the fusion of autophagosomes with lysosomes.[131]

Although limited data are available with regards to viral infections, several signalling pathways appear to act in concert to direct vitamin D-induced autophagy in microbial infections. It has been shown that vitamin D-induced autophagy can enhance the colocalization of mycobacterial phagosomes and autophagosomes in an LL37-dependent

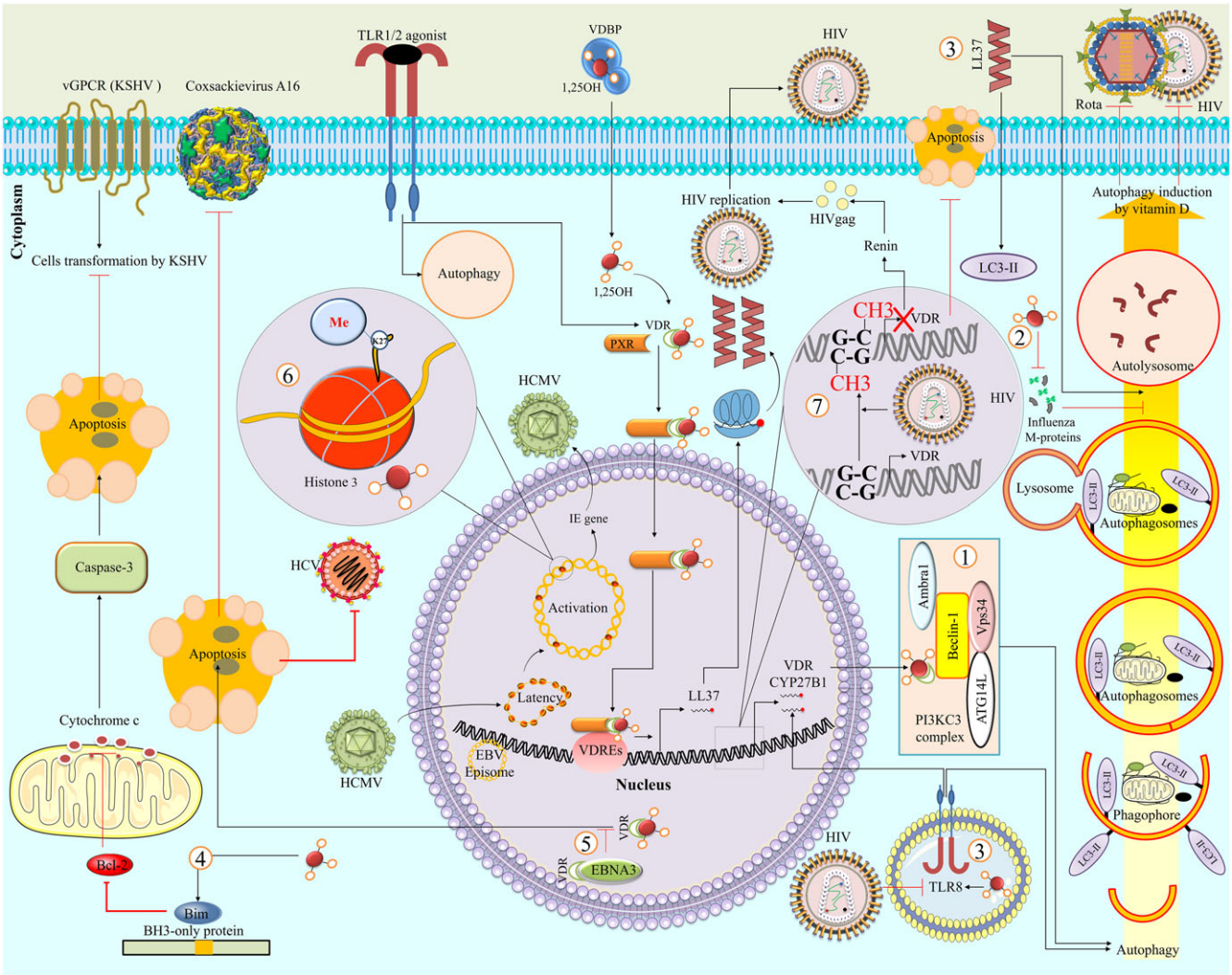

FIGURE 5 Autophagy, apoptosis, and epigenetic in viral infections and vitamin D.Vitamin D can directly or indirectly downregulate viral infections by (1) promoting autophagy-related components (PI3KC3 kinase complex), (2) downregulation of autophagy inhibitors (influenza M-proteins), (3) indirectly inducing autophagy (upregulation of LL37, and TLR8 stimulation), and (4) inducing apoptosis related factors (Bim), (5) which can also be inhibited by viral infections (EBV). Epigenetic elements and genetic polymorphisms are also involved in the complex interaction of vitamin D with viral infections. (6) this includes vitamin D modification of histone methylation (HCMV), and (7) viral enhancement of VDR promoter methylation (HIV)

TABLE 2 Interactions between viral infections and vitamin D

	Detailed mechanisms	Involved cells	Virus	Reference
Induction of antimicrobial peptide	Vitamin D induces LL37	Monocyte, macrophage, nonimmune cells (epidermis, gingiva, intestine, vagina, bladder, and lungs)	HIV-1	Bergman et al and Tangpricha et al[51,152]
			Vaccinia	Howell et al[52]
			HSV-1/2	Yasin et al and Howell et al[53,54]
			Influenza	Barlow et al[55]
			Rhino	Schögler et al[56]
			HCV	Gal-Tanamy et al and Matsumura et al[58,59]
	Vitamin D induces the production of HBDs	Macrophages, monocytes, DCs keratinocytes, and epithelial cells	HIV-1	Wang et al, Aguilar-Jimenez et al, and Doss et al[69,71,153]
			Influenza	Leikina et al[74,153]
			Rhino	Proud et al[73]
			Adeno	Bastian and Schäfer[72]
			Vaccinia	Howell et al[52]
Immunoregulatory function	Vitamin D increases specific viral immune response	CD4 and CD8 + T	EBV	Pender[81]
			HIV	Fawzi et al and McClelland et al[94,95]
			Influenza	Vimaleswaran et al[154]
	Vitamin D increases anti-inflammatory functions	IL10-producing cells and epithelial cells	EBV	Spach et al[84]
			RSV	Hansdottir et al[88]
			HCV	de Almeida et al[90]
			Influenza	Khare et al[106]
	Vitamin D inhibits the differentiation of B lymphocytes to plasma cells and class-switched memory B cells	B cells	EBV	Røsjø et al and Zhao et al[86,119]
	Vitamin D induces NF-kB-linked chemokines and cytokines	Epithelial cells	RSV	Hansdottir et al[88]
	Vitamin D up-regulates of TLR8	Macrophage	HIV	Campbell and Spector[103]
	Vitamin D impact HSV immunopathogenesis via TLR2/9 downregulation	HeLa cells	HSV-1	Kumar et al[104]
	Vitamin D induces secretion of recruitment of immune cells chemokines	Epithelial cells	Rhino	Brockman-Schneider[107]
	Vitamin D induces monocyte maturation/differentiation	Primary and cell line monocytes	HCMV	Wu and Miller[108]
Interaction with key cellular and viral factors	Vitamin D down-regulates of the NF-κB pathway, Vitamin D decreases NF-κB translocation to the nucleus, Vitamin D increases the expression of IκBa protein	Macrophages and endothelial cells transformed by the vGPCR	KSHV	Gonzalez-Pardo et al[115]
	Blocking transcription of VDR-responsive genes by EBNA-3	-	EBV	Yenamandra et al[117]
	Overlap between EBNA-2 and VDR-binding sites with MS regions	-	EBV	Ricigliano et al and Zhao et al[118,119]
	Vitamin D increases IκBα levels	Alveolar cells	RSV	Stoppelenburg et al[121]
	Vitamin D decreases levels of pSTAT-1, Vitamin D prevents pSTAT-1 translocation into the nucleus	Alveolar cells	RSV	Stoppelenburg et al[121]
	VDR can activate the LTR of HIV-1 in a ligand-dependent manner through nonclassical nuclear receptor transcriptional actions	HeLa, U937, and Cos-1 cells	HIV-1	Nevado et al[123]
	HIV p17 matrix protein induces CYP27B1 activity	Monocytes	HIV-1	Besancon et al[124]
	Vitamin D decreases influenza M proteins	Epithelial cells	Influenza	Khare et al[106]
	Vitamin D interference with NS3 function	HuH-7 cells	HCV	Matsumura et al[59]
	Vitamin D suppress the expression of apolipoprotein A1 and C3	Huh-7.5.1 cells	HCV	Murayama et al[128]
	Vitamin D decreases the concentrations of rotavirus antigen and nonstructural protein 4 (NSP4)	IPEC-J2 cells	Rota	Tian et al[134]
Induction of autophagy and apoptosis	Induction of autophagy by vitamin D	Macrophages	HIV	Campbell et al[132]
	Regulating autophagic maturation by vitamin D	IPEC-J2 and epithelial cells	Rota	Tian et al[134]
			Influenza	Khare et al[106]

(Continues)

TABLE 2 (Continued)

	Detailed mechanisms	Involved cells	Virus	Reference
	Inhibition vitamin D3-induced apoptosis by EBNA-3	Lymphoblastoid cells	EBV	Yenamandra et al[117]
	Increase of the pro-apoptotic BH3-only protein Bim by vitamin D	Endothelial cells and cells transformed by vGPCR	KSHV	Suares et al[136]
	VDR methylation provided the protection against apoptosis	HIV-induced T cell	HIV	Chandel et al[127]
	Vitamin D protects glioblastoma A172 cells by apoptosis	Glioblastoma cells	Coxsackie A	Qu et al[138]
Epigenetic	HIV-infected T cells have attenuated expression of VDR due to the enhanced cytosine methylation of the VDR promoter	T cells	HIV	Chandel et al[141]
	Modification of histone methylation in the immediate early (IE) gene promoter	Primary and cell line monocytes	HCMV	Van Damme et al[142]
Genetic polymorphisms	VDR-Apa1 genes higher in chronic HBV patients	-	HBV	Suneetha et al[143]
	VDR gene variant of genotype t/t associates with HBV clearance	-	HBV	Bellamy et al[155]
	Genetic variation of CYP2R1 influences host immune response in chronic hepatitis B infection	-	HBV	Thanapirom et al[148]
	ApaI polymorphism of VDR associated with the risk of HAM/TSP	-	HTLV-1	Saito et al[144]
	VDR gene polymorphisms were reported to be associated with disease progression in HIV-1 infected patients	-	HIV-1	Barber et al and de la Torre et al[156,157]
	VDBP rs7041-G and rs3733359-T variants associated with increased susceptibility to HCV infection	-	HCV	Xie et al[151]
	CYP27B1-1260 promoter polymorphism are also associated with chronic hepatitis C and poor response to interferon-alfa based therapy	-	HCV	Lange et al[149]
	VDR rs2228570 and CYP2R1 rs10741657 genes polymorphisms accurately assure sustained virological response (SVR) in naïve chronic hepatitis C patients	-	HCV	El-Derany et al[158]
	VDR variants (rs7975232-C, rs2239185-T, and rs11574129-T) contribute to a decreased susceptibility to HCV infection.	-	HCV	Wu et al[36]
	GC1s haplotype is thought to enhance RSV bronchiolitis in infancy and subsequent asthma development	-	RSV	Randolph et al[147]
	Children carrying the minor T allele of the VDR (Thr1Meth) single nucleotide polymorphisms (SNP) may predispose these children to RSV bronchiolitis	-	RSV	Kresfelder et al[145]

manner.[132]Moreover, physiological concentrations of vitamin D (25-170 nM) were shown to exert a potential inhibitory effect on replication of HIV and mycobacterium tuberculosis in macrophages through autophagy induction.[132] Stimulation of human macrophages with TLR8 agonists was also found to induce LL37 and autophagic flux via upregulating the expression of CYP27B1 and VDR.[132] Mycobacterial lipoprotein, a TLR2/1 agonist, can also exert antimycobacterial activities in human monocytes through autophagy induction that is thought to be dependent on functional VDR activation and cathelicidin expression.[133]

Vitamin D was shown to attenuate rotavirus infection via upregulating autophagic maturation and decreasing the concentration of NSP4, a viral enterotoxin.[134] Moreover, in influenza, a significant decrease of matrix proteins has been reported following pre- and post-treatment of influenza infected cells with calcitriol, with the M2 protein able to block the normal maturation of autophagosomes.[106,135]

Apoptosis is another mechanism by which vitamin D is suggested to play a role in EBV and KSHV infections (Figure 5).[117,127,136-138] It has been reported that EBNA-3 is capable of blocking the expression of VDR-dependent genes involved in growth inhibition and apoptosis.[117] Similarly, vitamin D treatment of endothelial cells and cells transformed by the vGPCR of KSHV was shown to increase the pro-apoptotic protein Bim through a caspase-3-dependent mechanism.[136]

1.5 | Epigenetic elements

The activity of VDR can be modulated epigenetically by DNA methylation or histone acetylation, which can be influenced by histone acetyl transferases (HATs) and histone deacetylases (HDACs).[139] The efficiency of vitamin D appears to be highly dependent on epigenetic modifications of its receptor. Although there is a relative paucity of data, vitamin D epigenetics have been suggested to play a role in HIV,[140] and HIV-infected T cells display low VDR expression due to enhanced cytosine methylation at VDR promoter.[141] Vitamin D may also induce the lytic phase of HCMV driven by monocyte maturation/differentiation, which may lead to a modification of histone methylation in the immediate early (IE) enhancer region of HCMV, resulting in the induction of immediate early gene expression.[108,142]

1.6 | Genetic polymorphism

Genetic polymorphism of VDR is thought to be associated with the clinical course of several viral infections. In this regard, the frequency of allelic distribution of VDR-apaI genes was reported to be significantly higher in chronic HBV patients with severe liver disease and the risk of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[143,144] As such, interference with VDR gene expression may influence susceptibility to RSV disease.[145,146] VDBP GC1s haplotype is thought to enhance RSV bronchiolitis in infancy and subsequent asthma development.[147] Moreover, CYP2R1 polymorphisms might be predictive of sustained HBeAg seroconversion after PegIFN therapy in chronic HBV infection.[148] Polymorphism in the CYP27B1 promoter and VDR were also found to be associated with chronic HCV, fibrosis, and poor response to IFN-alfa-based therapy.[149,150] A recent study conducted in a high-risk Chinese population suggest the role of VDBP rs7041-G and rs3733359-T variants in increased susceptibility to HCV infection.[151] Although these findings highlight the role of vitamin D-related polymorphisms in viral pathogenesis, it is not yet clear what might be the impact of these genetic polymorphisms on vitamin D metabolism in viral infections.

2 | CONCLUSION

The beneficial role of vitamin D in viral infections is well-described by several epidemiological studies, supporting the notion that higher levels of vitamin D are associated with better prognosis and improved outcomes. Although the mechanisms responsible for vitamin D function in the host immune system have been widely described, the interplay between viral infections and vitamin D status remains an intriguing area, and the potential interactions between viral infections and vitamin D appears to be more complex than previously thought. Induction of antimicrobial peptides, immunoregulatory function, interaction with cellular and viral factors, induction of autophagy and apoptosis, epigenetic elements, and genetic polymorphisms are the main underlying mechanisms by which vitamin D insufficiency could contribute to viral disease development (Table 2).

It would be of interest to investigate the global imprint that vitamin D can have on the immune signature of viral infections. The interplay between vitamin D and autophagy appears to be in its infancy particularly in the context of viral infections. As such, dissecting the molecular mechanisms by which vitamin D utilizes autophagy may provide new insights particularly for those who suffer from multifactorial autoimmune diseases. A detailed understanding of the biological actions of vitamin D and its crosstalk with genetic and epigenetic factors provides a rationale to stimulate investigation and management of different viral infections, particularly in the context of autoimmune diseases and cancer.

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