



Role of Vitamin D in the Immune System

D Vitamininin İmmun Sistemdeki Rolü

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Abstract

Vitamin D is suggested to be an important immune system regulator. 1,25 dihydroxyvitamin D (1,25(OH)₂D₃), which is the active form of vitamin D, decreases the proliferation of purified T-helper (Th)1 cells as well as the production of interferon (IFN) γ , interleukin (IL)-2, IL-5 and tumor necrosis factor-alpha (TNF- α). In Th2 cells, 1,25 (OH)₂D₃ stimulates IL-4 and transforming growth factor TGF production, which in turn may suppress inflammatory T cell activity. In the absence of vitamin D signaling, the T cell compartment has a potentially stronger Th1 phenotype. Furthermore, 1,25(OH)₂D₃ inhibits dendritic cell (DC) differentiation and maturation, leading to down-regulated expression of major histocompatibility complex class II molecules (MHC-II), co-stimulatory molecules and IL-12; enhances IL-10 production and promotes DC apoptosis. Because of these effects, 1,25(OH)₂D₃ inhibits DC-dependent T cell activation. In vitro, it is determined that 1,25(OH)₂D₃ stimulates phagocytosis and killing of bacteria by macrophages, but suppresses the antigen presenting capacity of these cells and dendritic cells. Additionally, Chen et al. have suggested that vitamin D might have a role in regulating antibody production. They have found that 1,25(OH)₂D₃ not only inhibits activated B cell proliferation but induces their apoptosis as well. *Türk Jem 2013; 17: 5-7*

Key words: Vitamin D, immune system, t cell, 1,25(OH)₂D₃, dendritic cell

Özet

Son yıllarda, vitamin D'nin immün sistemdeki düzenleyici rolü üzerinde durulmaktadır. Vitamin D'nin aktif formu olan 1,25 dihydroxy vitamin D (1,25(OH)₂D₃), T helper (Th)1 hücrelerinin çoğalmasını baskılar ve bu hücrelerden sitokin (interferon (IFN) γ , interleukin (IL)-2) üretimini azaltır. Th2 hücrelerinden ise IL-4 ve inflamatuvar T hücre aktivitesini baskılayan transforming growth factor üretimini artırır. Vitamin D uyarısı olmadığında T hücrelerinde, Th1 fenotipi baskındır. 1,25(OH)₂D₃ major histokompabilite antiijen-II (MHC-II) ekspresyonuna yol açan dendritik hücrelerin (DC) farklılaşmasını, olgunlaşmasını ve IL-12 sentezini baskılar, IL-10 sentezini ise artırır, DC lerin apoptozisini indukler. Böylece 1,25(OH)₂D₃ DC'e bağlı T hücre aktivasyonunu inhibe etmiş olur. İn vitro olarak 1,25(OH)₂D₃'ün bakterilerin makrofajlar tarafından öldürülmesini uyardığı diğer taraftan makrofajların ve DCLerin antiijen sunma kapasitelerini baskıladığı gösterilmiştir. Ayrıca Chen ve arkadaşları vitamin D'nin antikor üretiminin düzenlenmesinde de rol oynayabileceğini ileri sürmüş, çalışmalarında 1,25(OH)₂D₃'ün B hücrelerinin çoğalmasını baskılamakla kalmayıp, aynı zamanda B hücrelerinin apoptozunu indüklediğini de göstermiştir. *Türk Jem 2013; 17: 5-7*

Anahtar kelimeler: Vitamin D, immün sistem, T hücreleri, 1,25(OH)₂D₃, dendritik hücreler

Introduction

The best characterized effect of vitamin D is on the small intestine and the bone. In the small intestine, vitamin D increases the absorption of calcium by increasing the expression of a specific calcium channel. In bone, vitamin D induces the differentiation of pre-osteoclasts into mature osteoclasts, ultimately promoting removal of calcium and phosphorus from the bone (1-3).

Vitamin D enters the human body via two sources: exposure of the skin to sunlight and diet (1). Solar radiation in the UVB waveband (wavelength, 290 to 315 nm) converts 7-dehydrocholesterol to previtamin D₃ which is converted to vitamin D₃ (1-5).

Natural dietary sources of vitamin D are wild fresh salmon (800 IU of D₃ per 3.5 oz), cod liver oil (700 IU of D₃ per 1 tps), sun-dried Shiitake mushrooms (1600 IU of D₂ per 3.5 oz), fortified foods such

as milk (100 IU of D3 per 8 ox), and other supplements. Vitamin D2 is produced through the ultraviolet irradiation of ergosterol, and vitamin D3 is produced through the ultraviolet irradiation of 7-dehydrocholesterol. Both of those vitamin D forms are used as vitamin D supplements (5).

Vitamin D made in the skin (D3) or ingested (either D2 or D3) travels in the bloodstream binds to vitamin D-binding protein, and reaches the liver where it is converted to 25-hydroxyvitamin D3 [25(OH)D3]. This is the major circulating form of vitamin D, the one measured by clinical laboratories to determine the vitamin D status. A normal level of circulating 25(OH)D3 is between 20 and 80 ng/mL. Levels below 20 ng/mL are considered indicative of vitamin D deficiency. Vitamin 25(OH)D3 is biologically inactive and must be converted in the kidneys to the biologically active form, 1,25 dihydroxy vitamin D (1,25(OH)2D3) (5).

Until 1980, vitamin D has not been imagined to have a role in the functioning of the immune system (6).

The discovery of vitamin D receptor (VDR) in lymphocytes, promyelocytes, macrophages, dendritic cells (DC) and islet cells of pancreas resulted in the idea that vitamin D had functions beyond calcium and phosphorus metabolism and that idea prompted investigations into noncalcemic actions of the vitamin D hormone (6,7).

It has been shown that vitamin D has an important role in the regulation of the immune system. 1,25dihydroxyvitamin D3 (1,25(OH)2D3) has been determined to suppress the development of autoimmune diseases. However, it does not have any effect on immunity to infectious organisms and other immune system mediated-diseases such as experimental asthma (7). Dendritic cells, T helper 1 (Th1) and Th2 cells are direct targets of 1,25(OH)2D3 (8).

VDR is not found in appreciable amounts in the B lymphocyte, but in significant concentrations in the T lymphocytes and macrophages (6,9). However, its highest concentration is in the immature immune cells of the thymus and the mature CD8 T lymphocytes. Immune cells are able to synthesize and secrete 1,25(OH)2D3 as they contain 1α -hydroxylase enzyme, which is necessary for the final activation step in the conversion of vitamin D3 to the biological active form (10). The 1α -hydroxylase enzyme in immune cells is identical to the renal enzyme, but regulation of its expression and activity is different. Whereas the renal enzyme is principally under the control of calcemic and bone signals (such as parathyroid hormone and 1,25(OH)2D3, itself), the 1α -hydroxylase enzyme in the macrophage is primarily regulated by immune signals, interferon γ (IFN- γ) and toll-like receptor agonist which is the powerful stimulator of that enzyme (10). Many studies have shown that some autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, experimental autoimmune encephalomyelitis, type 1 diabetes, and inflammatory bowel disease (IBD) can be not only prevented but also suppressed by 1,25(OH)2D3 (6). Recent studies have shown significant association of vitamin D deficiency with obesity, type 2 diabetes mellitus and Hashimoto's thyroiditis (11-25).

Th1 cells secrete IFN- γ , interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF- α) and Th2 cells secrete IL-4 and IL-5. All of those cytokines are important for strong antibody-mediated immunity. Activation of Th1 cells is needed for cell-mediated immunity such

as host responses to intracellular pathogens and tumors. Th1 cells are misdirected against self proteins in autoimmune diseases such as type 1 diabetes mellitus. Th2 cells are essential in immune responses to extracellular pathogens such as bacteria and parasites. Dendritic cells, Th1 and Th2 cells are direct targets of 1,25(OH)2D3. Normally, expression of VDRs on quiescent CD4+ T cells is very low, but increases 5-fold after the activations of T cells (7,26). 1,25(OH)2D3 reduces the proliferation of purified Th1 cells and the productions of IFN γ , IL-2, IL-5 and TNF- α , but, induces IL-4, and transforming growth factor (TGFB) synthesis, which is able to suppress inflammatory T cell activity in Th2 cells (7,26). One of the evidences of that, a murine model of the human disease multiple sclerosis cannot be suppressed by 1,25(OH)2D3 in IL-4-deficient mice (11). The effects of 1,25(OH)2D3 on inhibition of the autoimmune diseases *in vivo* has been shown to depend on IL-2 (27) and IL-4 secretions (28). 1,25(OH)2D3 decreases Th1 cell cytokines, but increases secretion of IL-4 which is one of the Th2 cell cytokines. When vitamin D signaling is absent, Th1 phenotype is the strongest phenotype in T cell compartment (7). Furthermore, Abe et al. and Tanaka et al. determined that vitamin D can not only inhibit promyelocytes proliferation, but induces their differentiation into monocytes as well (6,29,30).

Vitamin D or VDR deficient hosts have high Th1 cell cytokine levels, although they have low levels of Th2 cell cytokines. When vitamin D signaling is absent, IBDs are more serious and asthma which is driven by Th2 cells does not develop. Results of recent studies suggest a model in which 1,25(OH)2D3 treatment for autoimmune diseases results in inhibition of Th1 cells proliferations and cytokine productions but induction of Th2 cells and Th2 cells cytokine synthesis (7,31). Moreover, 1,25(OH)2D3 inhibits DC differentiation and maturation, leading to down-regulated expression of MHC-II, co-stimulatory molecules and IL-12 and, enhances IL-10 production and promotes DC apoptosis. Because of those effects, 1,25(OH)2D3 inhibits DC-dependent T cell activation (32). *In vitro*, it has been determined that 1,25(OH)2D3 stimulates the phagocytosis and killing of bacteria by macrophages but suppresses the antigen presenting ability of those cells and DCs (33,34). IL-12 is produced by macrophages and DCs and is the major determinant of the direction in which the immune system will be activated, since it stimulates the development of CD4 Th1 cells and inhibits the development of Th2 cells. Inhibition of production of IL-12 by vitamin D *in vitro* and a shift from Th1 to Th2 predominance can also be observed after *in vivo* administration of 1,25(OH)2D3 (35,36).

VDR is not found in appreciable amounts in the B lymphocyte. However, Chen et al. (37) have suggested that vitamin D might play a role in regulating antibody production. They have found that 1,25(OH)2D3 not only inhibits activated B cells proliferations but induces their apoptosis as well.

In conclusion, vitamin D stimulates the phagocytosis and killing of bacteria by macrophages, but suppresses Th1 cell activation by inhibiting the antigen presenting capacity of macrophages and DCs. At the second stage, vitamin D inhibits the secretion of Th1 cytokines and increases IL-4 secretion of Th2 cell. Moreover, vitamin D is suggested to have effects on B lymphocytes proliferation, apoptosis and antibody production.

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