THE IMMUNOLOGICAL IMPLICATIONS OF THE NEW VITAMIN D METABOLISM

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ABSTRACT

Vitamin D is actually a neurohormone whose pleiotropic activities encompass regulation of calcium-phosphate metabolism, cell proliferation and immunomodulation. Starting from a cutaneous compound, 2 hydroxylation steps are required to produce the active form of vitamin D3, named calcitriol [1, 25-(OH)2-cholecalciferol]. The second hydroxylation step may occur at different tissues and cell types, including kidney, lung, prostate, brain, immune cells and placenta. Based on the advancing knowledge of Cytochrome P450 functions, a new conception of Vitamin D metabolism emerged. It implies that, depending on the site where the second hydroxylation step occurs, the active hormone can act as a calcium-phosphorus-homeostasis regulator, or an immune system modulator, or a cell proliferation and differentiation regulator. A detailed description of new Vitamin D metabolism and Vitamin D regulation of immune response is provided in this review.

Keywords*: vitamin D, metabolism, immune response, CYP450.*

DOI: 193/0393-6384_2018_6_251

Received *December 30, 2018;* ***Accepted*** *February 20, 2018*

Introduction

Vitamin D refers to as 2 compounds, Vitamin D2 and Vitamin D3, originating by two different precursors: Vitamin D2 derives from irradiation of the plant sterol, ergosterol, while Vitamin D3 originates from 7-deidro-cholesterol. Vitamin D2 derives only from the diet; conversely, Vitamin D3 mostly originates by the endogenous synthesis. The only significant sources of Vitamin D (D2 and D3) are fatty fish, animal liver, fish oils and egg yolks.

Despite the name, Vitamin D is actually a neurohormone whose pleiotropic activities encompass regulation of calcium-phosphate metabolism, cell proliferation and immunomodulation. Such differences in terms of biological roles played by the neurohormone can be explained by a relatively new conception of Vitamin D metabolism, which is illustrated below.

New vitamin D metabolism

Human Vitamin D3 undergoes activation starting from the action of ultraviolet B (UVB) action on the cutaneous compound, 7-deidro-cholesterol, producing cholecalciferol. Then, 2 hydroxylation steps at different sites are required to produce the active form of vitamin D3, named calcitriol [1, 25-(OH)2-cholecalciferol]. The first hydroxylation only occurs in the liver, where the enzyme 25-hydroxylase produces calcidiol [25-(OH)-cholecalciferol]. This represents the main circulating Vitamin D metabolite and is regarded as a marker of Vitamin D status. Circulating calcidiol reach several tissues and cell types, where it provides a local pre-hormone supply. A second hydroxylation step is required to produce the active hormone and is carried-out by the enzyme 1-alpha-hydroxylasis. Such hydroxylation may occur at different tissues and

cell types, including kidney, lung, prostate, brain, immune cells and placenta[1]. Depending on the site where the second hydroxylation step occurs, the active hormone can act as a calcium-phosphorus-homeostasis regulator, or an immune system modulator, or a cell proliferation and differentiation regulator. Thus, pleiotropic activities of Vitamin D can be summarized according to the location where the 1-alpha-hydroxylation takes place.

For instance, the regulation of calcium-phosphate metabolism totally depends on the kidney- 1-alpha-hydroxylases, originating a hormone with endocrine effects. Thus, reaching the gut, it makes the major contribution to calcium-phosphorus homeostasis; such 1-alpha-hydroxylases is strictly regulated by parathyroid hormone (PTH). Differently, Vitamin D- mediated immunomodulation refers to the calcitriol produced by 1-alpha-hydroxylases present on macrophage, monocyte, T and B lymphocyte, which release the hormone by a paracrine and autocrine secretion. Immune cells- 1-alpha-hydroxylases is tightly regulated by cytokines (IL-1, TNF, IFN-γ) but not by PTH.

Finally, tissues having their 1-alpha-hydroxylases are able to regulate their growth and differentiation by controlling their own proliferative activity due to the secretion of calcitriol with autocrine effects. 1-alpha-hydroxylasis (CYP27B1) is a Cytochrome P450 (CYP) superfamily enzyme. Strong efforts have been done to elucidate the role of CYPs, since they were mostly known to carry out oxidation/reduction reactions and liver drug catabolism[2]. Advancing knowledge in CYPs allowed the discovery of apoptotic role Vitamin D plays on selected cells, leading to consider the hormone as an anti-proliferative drug in cancer. Nowadays it is clearly known that CYP enzymes are totally responsible for Vitamin D intracellular metabolism. Finally, lung calcitriol is involved in challenging respiratory tract infections, which can be assessed by established biomarkers[3].

Vitamin D Receptors

Most of the roles played by Vitamin D3 depend on the nuclear Vitamin D Receptor (VDR). The discovery that cells of bone marrow, breast, brain, colon and immune system present VDR, opened a new perspective on the role of vitamin D apart from regulating calcium-phosphorus homeostasis.

Once Vitamin D3 binds VDR, neo-synthesis of mRNA and protein and cell proliferation take place. The interaction between VDR and the retinoic acid receptor (RXR) determines the activation of response elements (VDREs), located in the promoter region of several genes. The vitamin D/VDR-RXR-VDREs complex is deemed to regulate about 900 genes (4). Apart from immune cell types, prime location of VDR is the brain, thereby it is worth to vitamin D the definition of neurohormone[5].

Other Vitamin D receptors apart from VDR are known. A surface receptor named 1,25- (OH) 2D-MARRS (membran- associated rapid response steroid binding) or ERp57 / Grp58[6] mediates some non- genomic rapid actions of Vitamin D3, as regulation of adenylate cyclase activity, phospholipase C and C kinase. Moreover, a membrane VDR (MVDR), which is similar to the nuclear VDR (NVDR), can mediate other non-genomic rapid actions, as activation of the phosphatidylinositol 3-kinase and the endothelial nitric oxide synthase[7].

Vitamin D as a citokine

It is now accepted that Vitamin D resembles a cytokine, being both a transcription- and a growth factor for immune cells; further, the neurohormone displays some features that are common to cytokines, such as pleiotropy, synergy, redundancy and interaction with surface receptors[8]. Vitamin D plays a pivotal role in promoting innate immune response, by enhancing the production of antimicrobial agents by monocyte and neutrophils, and is able to modulate the specific immune response[9]. Concisely, Vitamin D plays four main activities as immune-modulator. Firstly, it acts skewing T cell to Th2 polarization, attenuating and stimulating Th1 and Th2 cell proliferation, respectively[10]. Indeed, vitamin D can inhibit the synthesis, secretion and release of anti- inflammatory cytokines produced by Th1 cells (IL-4 and IL-10), whilst inducing those of pro-inflammatory cytokines originated from Th2 cells (IL-1, TNF-α, IFN-γ)[11]. Secondarily, Vitamin D can suppress Th 17 cell production of IL-17, which appears to play a role in autoimmune diseases. Third, the hormone has been proved to promote self- tolerance[12]. Finally, Vitamin D contributes to T regulatory cells (Treg) differentiation[9]. The role of Vitamin D3 in innate and adaptive immune response emerged with the discovery that several immune cells express VDR, mainly after immune response activation. Macrophages, monocytes and B and T lymphocytes show, even during quiescence, a low expression of VDR, which increases considerably as a result of

inflammatory and immunological stimuli, transposed and amplified by the same cell types[13]. Due to the above reported evidence, either Vitamin D plasma levels or some VDR allelic variants have been largely investigated in immunological disorders. Although manifold studies have demonstrated an association between Vitamin D deficiency and several autoimmune diseases[14-18], not all immune disorders are linked to Vitamin D status[19,20]. Moreover, effects of Vitamin D supplementation are not univocally demonstrated to impact on autoimmune disease activity and progression[21]. How Vitamin D may facilitate the onset and/or progression of disease is uncertain, but evidence supports the hypothesis that Vitamin D deficiency is one of the environmental factors predisposing to the onset of autoimmune disease[22]. However, no causal effect has been ever demonstrated between Vitamin D insufficiency and deficiency and disease onset or progression, neither in inflammatory disease (metabolic and cardiovascular) nor in autoimmune diseases.

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