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Vitamin D actions on cell differentiation, proliferation and inflammation

Abstract

The most well-known function of vitamin D (1,25-$(OH)_2D_3$) is to maintain calcium and phosphate homeostasis and promote bone mineralization. However, apart from these traditional calcium-related actions, 1,25-$(OH)_2D_3$ is being increasingly recognized for its potent antiproliferative, pro-differentiation, and immunomodulatory roles. Along with these non-calcemic or non-classic actions of 1,25-$(OH)_2D_3$, new therapeutic actions of 1,25-$(OH)_2D_3$ have been discovered in recent years.

Keywords: cell differentiation and proliferation, inflammation, vitamin d

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Introduction

1,25-Dihydroxyvitamin D_3. 1,25(OH)2D3 is a multifunctional hormone that exerts its actions by binding to the vitamin D receptor (VDR), a member of the nuclear receptor superfamily. The number and variety of 1,25-$(OH)_2D_3$ target genes combined with the presence of the VDR in a high variety of tissues is reflected by the diversity of physiological actions of 1,25-$(OH)_2D_3$.[1] VDR was first discovered and cloned in chick intestine[2] and later demonstrated to be present in almost all human cells and tissues.[3] First and foremost, 1,25-$(OH)_2D_3$ is the major regulator of calcium and phosphate hemostasis and plays a pivotal role in ensuring bone integrity. This is often referred to as the "classic actions" of 1,25-$(OH)_2D_3$ and is mediated by fine-tuned interactions between parathyroid hormone (PTH), calcium and phosphate levels and 1,25-$(OH)_2D_3$ itself.[4]

The presence of the VDR in tissues that not participate in mineral ion homeostasis led to the discovery of several other functions for the versatile vitamin D hormone. The ability of 1,25-$(OH)_2D_3$ to inhibit growth and promote differentiation of various cell types has suggested diverse functions in preventing cancers, modulating the immune system, and controlling different endocrine functions.[5]

Vitamin d in cell differentiation and proliferation

In the last years, a significant number of clinical and experimental studies have demonstrated the participation of 1,25-$(OH)_2D_3$ in cell differentiation and in the restoration of cell differentiation in neoplastic cells (non-classic actions).[6,7] When 1,25-$(OH)_2D_3$ binds to its VDR receptor, forming the 1,25-$(OH)_2D_3$/VDR complex, it has specific actions even before cell differentiation begins. It enhances the expression and/or activity of various brush border enzymes, such as alkaline phosphatase and maltase, inducing the formation of microvilli.[8] In addition, 1,25-$(OH)_2D_3$ increases the expression of various components of cell adhesion such as occludin, occlusion zonula 1 and 2 (zonula occludens) and claudins 2 and 12 in tight junctions, E-cadherin in adherent joints and plectine in hemidesmosomes, which are essential structures for the differentiation and maintenance of the epithelial phenotype.[9] Nakamura et al.,[10] 2011 showed also the participation of 1,25-$(OH)_2D_3$ in the expression of proteins involved in cell motility, adhesion and invasion, such as Filamin A, which has nuclear role in the regulation of nuclear repair and in the epithelial-mesenchymal transition (EMT).[10] The exact mechanism on how 1,25-$(OH)_2D_3$ regulates cell proliferation and differentiation is not yet well understood but it is known that it can control cell replication by regulating genes involved in the cell cycle including p19, p27, p21 and p53.[11] It interferes with, and inactivate the kinase-dependent cycle complex in the G1 phase, causing the cell to remain in the G1 phase, not moving further on the cell cycle. 1,25-$(OH)_2D_3$ also decreases the degradation of p27, which will inhibit proliferation and cell migration and modulates apoptosis.[12] These actions are complex and involve transcriptional and post-transcriptional mechanisms and may also act on many factors via kinase/cyclin-dependent cyclin systems (TGF-β, IGFBP3 and EGFR).[13]

Recent observations have demonstrated that many tissues and cells not only express the VDR but also may present 1α-hydroxylase, and therefore are capable of the production of 1,25-$(OH)_2D_3$, that can act by the autocrine or paracrine ways.[14] Such tissues and cells include the breast; colon; prostate; macrophages; and cells of the vascular system, and potentially other sites. The role of this extra renal 1α-hydroxylase, with the production of 1,25-$(OH)_2D_3$ in these tissues, is not well understood, but a variety of *in vitro* studies indicate that this process may be involved in the regulation of cell growth and differentiation.[15]

Vitamin d in inflammation

1,25-$(OH)_2D_3$ deficiency has also been linked to the increase in the intensity of the inflammatory process under pathological conditions.[16] The 1,25-$(OH)_2D_3$ has an anti-inflammatory effect on the inflammatory profile of mono-cytes, down-regulating the expression and production of several pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, and IL-8.[17] As inflammation is triggered, cytokines are released that activate endothelial cells, which in turn release additional pro inflammatory cytokines and present chemokines and adhesion molecules on their luminal surface. Various *in vitro* cell culture studies have reported that 1,25$(OH)_2D_3$ decreased lipopolysaccharide (LPS), a prototypical endotoxin, or advanced glycation end product-induced cytokine (e.g., IL-6) and chemokine (e.g., RANTES) expression and secretion from HUVEC[18] and from human microvascular endothelial cells (HMEC).

Panichi et al.,[19] investigated the role of 1,25-$(OH)_2D_3$ in a rat model with mesangial nephritis, and found that 1,25-$(OH)_2D_3$ treatment reduced IL-6 cytokine, macrophage infiltration, apoptosis. They also demonstrated its antiproliferative effect by attenuating immune

labeling to proliferating cell nuclear antigen (PCNA), as well as its anti-inflammatory activities and effects on cell differentiation, proliferation and apoptosis.[19]

Data from experimental and clinical studies published in recent years suggest that 1,25-$(OH)_2D_3$ protect the kidney by targeting two major pathways that promote renal damage and progression of kidney disease: the local renin angiotensin system (RAS) and the NF-κB pathway.[20] 1,25-$(OH)_2D_3$ acts as a negative regulator of renin gene expression via cAMP response element-binding protein (CREB) inhibition, which is required for the expression of rennin.[21] In an experimental model of diabetic nephropathy, it was demonstrated that 1,25-$(OH)_2D_3$ also has a suppressive effect on the expression of angiotensin converting enzyme 1 and 2(ACE), demonstrating the renoprotective action of in 1,25-$(OH)_2D_3$ on the modulation of RAS.[22] The effects of the host 25(OH)D levels could extend beyond the macrophage, as lung epithelial cells have been demonstrated to express 1α-hydroxylase, and convert 25(OH)D into 1,25$(OH)_2D_3$ leading to expression of cathelicidin.[23] These authors demonstrated that a host deficient in 25(OH)D could present impaired innate immune responses and reduced innate immune effector cells resulting in increased susceptibility to infection. Therefore, returning circulating levels of 25(OH)D to normal could potentially restore their host defense mechanisms.

Conclusion

Recent biochemical, genetic, molecular, and physiological studies have established 1,25$(OH)_2D_3$ as a negative endocrine regulator of the RAS and *inflammatory cytokines.* This discovery reveals an important physiological function of the vitamin D endocrine system. As such, long term 1,25$(OH)_2D_3$ deficiency can lead to over activation of the RAS and consequently activate the pathways of inflammation. Because of the broad involvement of these pathways in inflammation and the development of various diseases, this finding has invaluable pathophysiological and therapeutic implications. It provides a mechanistic insight into the ever-increasing epidemiological and clinical evidence linking 1,25$(OH)_2D_3$ deficiency to renal and cardiovascular problems in the general population. It also provides a molecular basis to explore the therapeutic potentials of 1,25$(OH)_2D_3$ in the prevention and intervention on such diseases.

Conflicts of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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