

Vitamin D actions on cell differentiation, proliferation and inflammation

Abstract

The most well-known function of vitamin D (1,25-(OH)₂D₃) is to maintain calcium and phosphate homeostasis and promote bone mineralization. However, apart from these traditional calcium-related actions, 1,25-(OH)₂D₃ 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)₂D₃, new therapeutic actions of 1,25-(OH)₂D₃ have been discovered in recent years.

Keywords: cell differentiation and proliferation, inflammation, vitamin d

Volume 6 Issue 5 - 2017

Lucas Ferreira de Almeida, Terezila Machado Coimbra

Department of Physiology of Ribeirão Preto Medical School, University of São Paulo, Brazil

Correspondence: Lucas Ferreira de Almeida, Avenida dos Bandeirantes, 3900, 14049-900 – Ribeirão Preto, SP, Brazil, Tel +55 16 3315 3021, Email lucas_fedameda@hotmail.com

Received: March 26, 2017 | **Published:** April 28, 2017

Introduction

1,25-Dihydroxyvitamin D₃, 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)₂D₃ 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)₂D₃.¹ VDR was first discovered and cloned in chick intestine² and later demonstrated to be present in almost all human cells and tissues.³ First and foremost, 1,25-(OH)₂D₃ 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)₂D₃ and is mediated by fine-tuned interactions between parathyroid hormone (PTH), calcium and phosphate levels and 1,25-(OH)₂D₃ 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)₂D₃ 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)₂D₃ in cell differentiation and in the restoration of cell differentiation in neoplastic cells (non-classic actions).^{6,7} When 1,25-(OH)₂D₃ binds to its VDR receptor, forming the 1,25-(OH)₂D₃/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)₂D₃ 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)₂D₃ 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)₂D₃ 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)₂D₃ 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)₂D₃, 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)₂D₃ 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)₂D₃ deficiency has also been linked to the increase in the intensity of the inflammatory process under pathological conditions.¹⁶ The 1,25-(OH)₂D₃ 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)₂D₃ 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 HUVEC¹⁸ and from human microvascular endothelial cells (HMEC).

Panichi et al.,¹⁹ investigated the role of 1,25-(OH)₂D₃ in a rat model with mesangial nephritis, and found that 1,25-(OH)₂D₃ 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)₂D₃ 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)₂D₃ acts as a negative regulator of renin gene expression via cAMP response element-binding protein (CREB) inhibition, which is required for the expression of renin.²¹ In an experimental model of diabetic nephropathy, it was demonstrated that 1,25-(OH)₂D₃ also has a suppressive effect on the expression of angiotensin converting enzyme 1 and 2 (ACE), demonstrating the renoprotective action of 1,25-(OH)₂D₃ 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)₂D₃ 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)₂D₃ 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)₂D₃ 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)₂D₃ 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)₂D₃ 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.

Acknowledgments

None.

Funding

None.

References

1. Reichrath J, Zouboulis CC, Vogt T, et al. Targeting the vitamin D endocrine system (VDES) for the management of inflammatory and malignant skin diseases: An historical view and outlook. *Rev Endocr Metab Disord*. 2016;17(3):405–417.
2. Baker AB, McDonnell DP, Hughes M, et al. Cloning and expression of full-length cDNA encoding human vitamin D receptor. *Proc Natl Acad Sci U S A*. 1988;85(10):3294–3298.
3. Bouillon R, Carmeliet G, Verlinden L, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev*. 2008;29:726–776.
4. Holick MF. Vitamin D Deficiency. *N Engl J Med*. 2007;357(3):266–281.
5. Holick MF. Vitamin D, Sunlight and Cancer Connection. *Anticancer Agents Med Chem*. 2013;13(1):70–82.
6. Feldman D, Krishnan AV, Swami S, et al. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer*. 2014;14(5):342–357.
7. Höbaus J, Thiem U, Hummel DM, et al. Role of calcium, vitamin d, and the extrarenal vitamin d hydroxylases in carcinogenesis. *Anticancer Agents Med Chem*. 2013;13(1):20–35.
8. Fujita H, Sugimoto K, Inatomi S, et al. Tight junction proteins claudin-2 and -12 are critical for vitamin D-dependent Ca²⁺ absorption between enterocytes. *Mol Biol Cell*. 2008;19(5):1912–1921.
9. Pálmer HG, González-Sancho JM, Espada J, et al. Vitamin D₃ promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of β-catenin signaling. *J Cell Biol*. 2001;154(2):369–387.
10. Nakamura F, Stossel TP, Hartwig JH. The filamins: organizers of cell structure and function. *Cell Adh Migr*. 2011;5(2):160–169.
11. Wang QM, Jones J.B, Studzinski GP. Cyclin-dependent kinase inhibitor p27 as a mediator of the G1-S phase block induced by 1,25-dihydroxyvitamin D₃ in HL60 cells. *Cancer Res*. 1996;56(2):264–267.
12. Peng L, Malloy PJ, Feldman D. Identification of a functional vitamin D response element in the human insulin-like growth factor binding protein-3 promoter. *Mol Endocrinol*. 2004;5(5):1109–1119.
13. Yamada PM, Lee K W. Perspectives in mammalian IGFBP-3 biology: local vs. systemic action. *Am J Physiol Cell Physiol*. 2009;296(5):954–976.
14. Morris HA, Anderson PH. Autocrine and Paracrine Actions of Vitamin D. *Clin Biochem Rev*. 2010;31(4):129–138.
15. Adams JS, Hewison M. Extrarenal Expression of the 25-Hydroxyvitamin D-1-Hydroxylase. *Arch Biochem Biophys*. 2012;523(1):95–102.
16. Ferder M, Inserra F, Manucha W, et al. The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system. *Am J Physiol Cell Physiol*. 2013;304(11):1027–1039.
17. Wöbke TK, Sorg BL, Steinhilber D. Vitamin D in inflammatory diseases. *Front Physiol*. 2014;5:244.
18. Talmor Y, Bernheim J, Klein O, et al. Calcitriol blunts pro-atherosclerotic parameters through NFκB and p38 in vitro. *Eur J Clin Invest*. 2008;38(8):548–554.
19. Panichi V, Migliori M, Taccola D, et al. Effects of 1,25(OH)₂D₃ in experimental mesangial proliferative nephritis in rats. *Kidney Int*. 2001;60(1):87–95.
20. Li YC. Renoprotective effects of vitamin D analogs. *Kidney Int*. 2010;8(2):134–139.
21. Yuan W, Pan W, Kon J, et al. 1,25-Dihydroxyvitamin D₃ Suppresses Renin Gene Transcription by Blocking the Activity of the Cyclic AMP Response Element in the Renin Gene Promoter. *Journal of Biol Chem*. 2007;282(41):29821–29830.
22. Lin M, Gao P, Zhao T, et al. Calcitriol regulates angiotensin-converting enzyme and angiotensin converting-enzyme 2 in diabetic kidney disease. *Mol Biol Rep*. 2016;43(5):397–406.
23. Hansdottir S, Monick MM, Hinde SL, et al. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. *J Immunol*. 2008;181(10):7090–7099.