Molecular and Cellular Endocrinology 453 (2017) 79–87

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

The endocrine vitamin D system in the gut

Antonio Barbáchano, Asunción Fernández-Barral, Gemma Ferrer-Mayorga, Alba Costales-Carrera, María Jesús Larriba, Alberto Muñoz*

Instituto de Investigaciones Biomédicas "Alberto Sols", Consejo Superior de Investigaciones Científicas - Universidad Autónoma de Madrid, E-28029 Madrid, Spain

ARTICLE INFO

Article history:
Received 5 October 2016
Received in revised form
28 November 2016
Accepted 28 November 2016
Available online 29 November 2016

Keywords:
Vitamin D
Gut homeostasis
Inflammatory bowel diseases
Gut microbiota
Colorectal cancer

ABSTRACT

The active vitamin D metabolite 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) has important regulatory actions in the gut through endocrine and probably also intracrine, autocrine and paracrine mechanisms. By activating the vitamin D receptor (VDR), which is expressed at a high level in the small intestine and colon, $1,25(OH)_2D_3$ regulates numerous genes that control gut physiology and homeostasis. $1,25(OH)_2D_3$ is a major responsible for epithelial barrier function and calcium and phosphate absorption, and the host's defense against pathogens and the inflammatory response by several types of secretory and immune cells. Moreover, recent data suggest that $1,25(OH)_2D_3$ has a regulatory effect on the gut microbiota and stromal fibroblasts. Many studies have linked vitamin D deficiency to inflammatory bowel diseases (ulcerative colitis and Crohn's disease) and to an increased risk of colorectal cancer, and the possible use of VDR agonists to prevent or treat these diseases is receiving increasing interest.

1. Introduction

For a long time, the gut has been known to be a major target tissue of vitamin D. 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), the hormonal vitamin D metabolite from the bloodstream (endocrine action) or locally produced from circulating $25(OH)D_3$ within intestinal cells expressing the enzyme $25(OH)D_3$-1α-hydroxylase/cytochrome P_{450} CYP27B1 (intracrine, autocrine and paracrine action), is a critical regulator of gut physiology and homeostasis (Fig. 1). $1,25(OH)_2D_3$ is crucial for Ca^{2+} and phosphate absorption and for epithelial integrity/barrier function and it contributes to detoxification and protection against infection (Christakos et al., 2016). Accordingly, the high affinity vitamin D receptor (VDR), a predominantly nuclear protein that regulates gene expression, is expressed in the small and large intestine/colon by epithelial and fibroblastic cells and by B-lymphocytes, T-lymphocytes ($CD4^+$ and $CD8^+$), macrophages and dendritic cells (Veldman et al., 2000). Remarkably, VDR levels are higher in intestinal epithelial cells than in other tissues and cell types (Yamamoto et al., 1999). All intestinal cell types also express CYP27B1, in many cases together with VDR, which supports intracrine, autocrine or paracrine effects of $1,25(OH)_2D_3$ (Adams and Hewison, 2008; Kundu et al., 2014). $1,25(OH)_2D_3$ is one of the main regulators of the human genome controlling the transcription rate of hundreds of genes in a tissue-specific fashion *via* its binding and modulation of VDR activity, as a transcription factor within the cell nucleus and as an inducer of non-genomic signaling in the cytosol (Ordóñez-Morán et al., 2008). Thus, the effects of $1,25(OH)_2D_3$ in the gut are mediated by the proteins encoded by its target genes, a significant proportion of which are specific to this organ.

The importance of $1,25(OH)_2D_3$ action in the gut is supported by the association of multiple pathologies with vitamin D deficiency, such as loss of Ca^{2+} homeostasis (rickets and osteomalacia), inflammatory bowel diseases (IBD: ulcerative colitis and Crohn's disease) and increased risk of colorectal cancer (CRC) (Fig. 2). Mice lacking Vdr ($Vdr^{-/-}$) develop hypocalcemia and hypophosphatemia and severe bone malformation together with other defects, but no gross abnormalities in the gut. However, these $Vdr^{-/-}$ mice show high levels of markers of cell proliferation and DNA oxidative damage in the colon (Kallay et al., 2002).

Abbreviations: $1,25(OH)_2D_3$, 1α,25-dihydroxyvitamin D_3; CDX-2, Caudal-related homeobox transcription factor 2; CRC, Colon/colorectal cancer; IBD, Inflammatory bowel diseases; IL, Interleukin; IκB, Inhibitor of κB; LCA, Lithocholic acid; miR, MicroRNA; MLCK, Myosin light chain kinase; NFκB, Nuclear factor κB; TER, Trans-epithelial resistance; TGF-β, Transforming growth factor β; TNF-α, Tumor necrosis factor-α; VDR, Vitamin D receptor; ZO, *Zonula occludens*.

* Corresponding author. Instituto de Investigaciones Biomédicas "Alberto Sols", Arturo Duperier, 4, E-28029 Madrid, Spain.
E-mail address: amunoz@iib.uam.es (A. Muñoz).

http://dx.doi.org/10.1016/j.mce.2016.11.028
0303-7207/

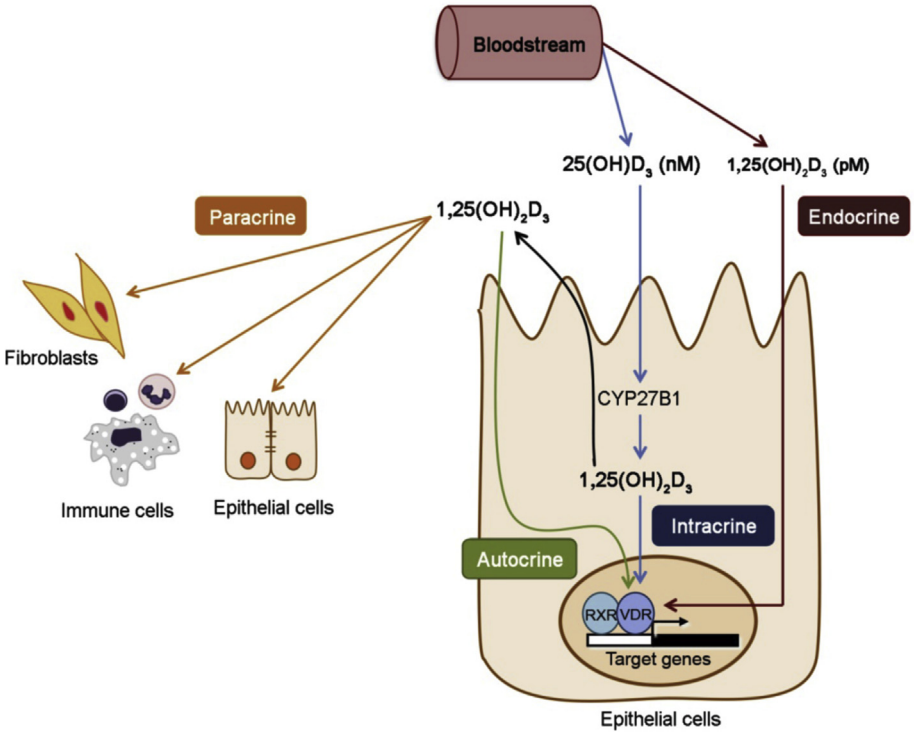

Fig. 1. Diagram of the different types of actions of $1,25(OH)_2D_3$ in the gut. Circulating $25(OH)D_3$ (nanomolar range) and $1,25(OH)_2D_3$ (picomolar range) reach intestinal cells where the latter binds VDR and regulates the transcription of target genes (endocrine action). Intestinal cells express CYP27B1 that converts $25(OH)D_3$ into $1,25(OH)_2D_3$, which can act within the synthesizing cell (intracrine action) or be secreted and act on the same cell (autocrine action) or on neighboring cells (paracrine action) as VDR is expressed in all cell types in the intestine.

2. Ca^{2+} and phosphate absorption

Control of Ca^{2+} homeostasis in the organism is the most classical and probably the principal role of $1,25(OH)_2D_3$. In conditions of low Ca^{2+}, high level of $1,25(OH)_2D_3$ is generated from $25(OH)D_3$, due to induction of CYP27B1 in the kidney by the action of parathyroid hormone. Conversely, high Ca^{2+} inhibits $1,25(OH)_2D_3$ synthesis, as does a high level of $1,25(OH)_2D_3$ itself. As mentioned above, gut epithelial and immune cells also express CYP27B1, and thus synthesize $1,25(OH)_2D_3$ that acts intracrinally, autocrinally and/or paracrinally on neighboring cells. The homeostatic action of $1,25(OH)_2D_3$ on Ca^{2+} occurs in bone, kidney and, predominantly, in the intestine, where $1,25(OH)_2D_3$ is essential for Ca^{2+} absorption in basically all segments. Whether and/or to what extent intestinal

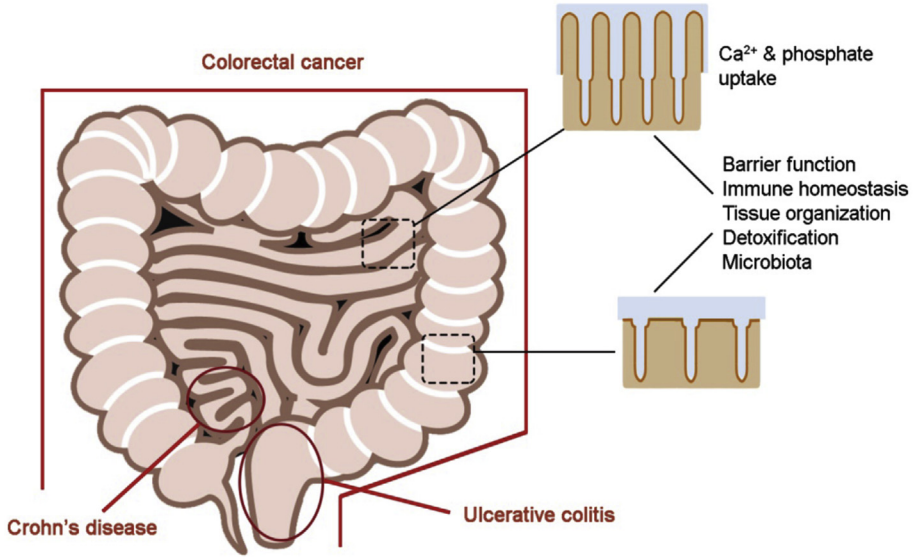

Fig. 2. Diagram depicting the main regulatory actions of $1,25(OH)_2D_3$ in the small intestine and colon. Some diseases associated with dysfunction of the vitamin D system in the gut are depicted (in red).