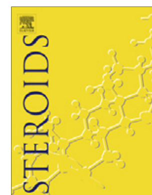
Steroids 78 (2013) 127–136

Contents lists available at SciVerse ScienceDirect

Steroids

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



Review

Vitamin D receptor signaling mechanisms: Integrated actions of a well-defined transcription factor

Carsten Carlberg [a,*], Moray J. Campbell [b]

[a] School of Medicine, Institute of Biomedicine, University of Eastern Finland, P.O. Box 1627, FIN-70210 Kuopio, Finland
[b] Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Buffalo, NY 14263, USA

ARTICLE INFO

Article history:
Received 3 September 2012
Received in revised form 19 September 2012
Accepted 27 October 2012
Available online 23 November 2012

Keywords:
Chromatin
Gene regulation
Genome-wide view
Nuclear receptor
Vitamin D
Vitamin D receptor

ABSTRACT

The main physiological actions of the biologically most active metabolite of vitamin D, 1α,25-dihydroxyvitamin D_3 (1α,25$(OH)_2D_3$), are calcium and phosphorus uptake and transport and thereby controlling bone formation. Other emergent areas of 1α,25$(OH)_2D_3$ action are in the control of immune functions, cellular growth and differentiation. All genomic actions of 1α,25$(OH)_2D_3$ are mediated by the transcription factor vitamin D receptor (VDR) that has been the subject of intense study since the 1980's. Thus, vitamin D signaling primarily implies the molecular actions of the VDR. In this review, we present different perspectives on the VDR that incorporate its role as transcription factor and member of the nuclear receptor superfamily, its dynamic changes in genome-wide locations and DNA binding modes, its interaction with chromatin components and its primary protein-coding and non-protein coding target genes and finally how these aspects are united in regulatory networks. By comparing the actions of the VDR, a relatively well-understood and characterized protein, with those of other transcription factors, we aim to build a realistic positioning of vitamin D signaling in the context of other intracellular signaling systems.

© 2012 Elsevier Inc. All rights reserved.

Contents

1. Introduction . . . 128
2. Perspective 1: VDR is a member of a transcription factor family . . . 128
3. Perspective 2: Genome-wide binding of VDR . . . 130
4. Perspective 3: Genomic DNA-binding modes of the VDR . . . 130
5. Perspective 4: VDR in dynamic interactions with chromatin components . . . 131
6. Perspective 5: Primary VDR target genes . . . 132
7. Perspective 6: VDR as a module component . . . 133
8. Conclusions . . . 133
Acknowledgements . . . 134
References . . . 134

Abbreviations: 1α,25$(OH)_2D_3$, 1α,25-dihydroxyvitamin D_3; 25$(OH)D_3$, 25-hydroxyvitamin D_3; ALOX5, arachidonate 5-lipoxygenase; AR, androgen receptor; CAMP, cathelicidin anti-microbial peptide; CCNC, cyclin C; CDKN1A, cyclin-dependent kinase inhibitor 1A; CoA, co-activator; CoR, co-repressor; ChIP, chromatin immunoprecipitation; ChIP-seq, ChIP coupled with massive parallel sequencing; CYP, cytochrome P450; DBD, DNA-binding domain; DIO1, thyroxine deiodinase type I; DR3, direct repeat spaced by 3 nucleotides; ER, estrogen receptor; FXR, farnesoid X receptor; GLDN, gliomedin; GR, glucocorticoid receptor; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDM, histone demethylase; HMT, histone methyltransferase; IGFBP, insulin-like growth factor binding protein; KLK3, kallikrein 3; LBD, ligand-binding domain; LXR, liver X receptor; miRNA, micro RNA; MR, mineralocorticoid receptor; PR, progesterone receptor; RAR, retinoic acid receptor; RE, response elements; RXR, retinoid X receptor; SP100, SP100 nuclear antigen; TFF1, trefoil factor 1; TR, thyroid hormone receptor; TSS, transcription start site; VDR, vitamin D receptor; VDRE, vitamin D response element.

* Corresponding author. Tel.: +358 40 355 3062.
E-mail address: carsten.carlberg@uef.fi (C. Carlberg).

0039-128X/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.steroids.2012.10.019

1. Introduction

The micronutrient vitamin D is essential for maintenance of health [1]. The most abundant form of vitamin D is 25-hydroxyvitamin D_3 (25(OH)D_3), the serum concentrations of which indicate the vitamin D status of a human individual [2]. The most biologically active vitamin D metabolite is the secosteroid 1α,25$(OH)_2D_3$, which acts as a pleiotropic endocrine hormone and influences many physiological processes [3]. For example, severe vitamin D deficiency leads to rickets, as 1α,25$(OH)_2D_3$ is essential for adequate Ca^{2+} and P_i absorption from the intestine and hence for bone formation [4].

An appreciation of the 1α,25$(OH)_2D_3$ endocrine system precedes the isolation of the VDR by well over 400 years as rickets was first described in the beginning of the 17th century. However, the molecular etiology for rickets remained unresolved until the beginning of the 20th century, when it was discovered that the dietary deficiency that caused rickets could be ameliorated by fish oil extracts and that the active ingredient was identified as vitamin D_3 [1]. Moreover, it was found that rickets could be cured by exposure to UV radiation. The analysis of 1α,25$(OH)_2D_3$ metabolism and the identification of 25(OH)D_3 in the 1960's [4] was followed by the identification of vitamin D-binding proteins in the 1970's [5,6] and the cloning of the VDR (also referred to as NR1I1 in the generic nuclear receptor terminology) in 1988 [7]. All this leads to a functional understanding of the vitamin D endocrine system.

In the subsequent decades remarkable strides have been made in describing the diverse biology that the VDR participates in. Researchers accommodated this diversity of biological actions by separating functions into the so-called "classical" actions, i.e. the regulation of serum calcium levels [8], and "non-classical" actions, i.e. everything else that includes control of metabolism, cellular growth and immune functions [9]. In particular, immuno-regulatory properties of 1α,25$(OH)_2D_3$ may be important, as low 25(OH)D_3 levels are associated with poor immune function and increased disease susceptibility [10]. Perhaps now these views are beginning to be consolidated into more unified views of the actions of the VDR.

Although a number of rapid and non-genomic actions of 1α,25$(OH)_2D_3$ have been described [11], the vast majority of the effects of the hormone are mediated by the VDR, which is the only protein that binds 1α,25$(OH)_2D_3$ effectively at sub-nanomolar concentrations [12]. This simplifies the understanding of vitamin D signaling, since the physiological effects of the hormone largely overlap with the actions of the transcription factor VDR.

Taken together, the VDR system can be viewed as a comprehensively understood transcription factor in terms of both mechanistic insight and phenotypic consequences. In this review, we therefore focus on VDR and its actions from multiple perspectives. We will (i) illuminate VDR as a transcription factor and member of the nuclear receptor superfamily, (ii) describe VDR's genome-wide locations and DNA-binding modes, (iii) analyze VDR's dynamic interactions with chromatin modifiers and other nuclear co-factors, (iv), address VDR's primary protein-coding and non-protein coding target genes and (v) delineate these roles and actions of VDR as a modular component in a regulatory network. Finally we will consider these regulatory networks integrated with the actions of other transcription factors, and thereby position the VDR, and its ligand 1α,25$(OH)_2D_3$, into the complex signaling system of human tissues and cell types.

2. Perspective 1: VDR is a member of a transcription factor family

In humans there are approximately 1900 classical transcription factors, i.e. proteins that sequence-specifically contact genomic DNA [13]. VDR is one of these DNA-binding transcription factors, but has an important additional property, which it shares only with some other members of the nuclear receptor superfamily: VDR can get specifically activated by low nanomolar concentrations of a small lipophilic molecule in the approximate size and molecular weight of cholesterol [14]. This property is shared with the nuclear receptors for the steroid hormones estradiol (ERα and ERβ), testosterone (AR), progesterone (PR), cortisol (GR) and mineralocorticoids (MR), for the vitamin A derivative all-*trans* retinoic acid (RARα, RARβ and RARγ) and for the thyroid hormone triiodothyronine (TRα and TRβ). Moreover, also a number adopted orphan members of the nuclear receptor superfamily, such as retinoid X receptors (RXRs) α, β, and γ, peroxisome proliferator-activated receptors (PPARs) α, δ, and γ, liver X receptors (LXR) α and β and farnesoid X receptor (FXR), show a similar mode of action, but their natural ligands, for example, 9-*cis* retinoic acid, fatty acids, oxysterols and bile acids, respectively, to date have not been considered as classical endocrine hormones and are in most cases bound by their respective receptors with far lower affinity and specificity [15].

The 48 human members of the nuclear receptor superfamily are characterized by a highly conserved DNA-binding domain (DBD) and a structurally conserved ligand-binding domain (LBD) [16]. The lower part of the LBD of all ligand-activated nuclear receptors contains a ligand-binding pocket of 400–1400 $Å^3$ in volume, in which the respective ligands are specifically bound [17]. The interior surface of these pockets is formed by the side chains of mostly non-polar amino acids and thereby complements the lipophilic character of the ligands [18].

All nuclear receptors have a similar mode of action. Therefore, a number of mechanisms that were identified, for example with ERs, apply also for the VDR. For example, ligand specificity is achieved through a limited number of stereo-specific polar contacts that include the so-called anchoring points and the actual shape of the pocket. Nuclear receptors that bind their specific ligand with high affinity, such as VDR and ERs, have a relatively small ligand-binding pocket, which is filled to a high percentage by ligand, while adopted orphan nuclear receptors, such as PPARs and LXRs, have a significantly larger ligand-binding pocket, which is filled to a far lower percentage by their ligand molecules [17].

As observed with other transcription factors, the DBD of the VDR cannot contact more than six nucleotides within the major groove of genomic DNA. Binding sites of monomeric nuclear receptors are therefore hexameric sequences and most members of the superfamily share consensus on the sequence RGKTSA (R = A or G, K = G or T, S = C or G). However, the DNA-binding affinity of monomeric VDR is insufficient for the formation of a stable protein–DNA complex and therefore the VDR has to complex with a partner protein, in order to achieve efficient DNA binding. The predominant partner of VDR is the nuclear receptor RXR [19].

Steric constraints allow dimerization of nuclear receptor DBDs only on DNA-binding sites that contain properly spaced hexameric binding motifs; these sequences are also referred to as response elements (REs). An asymmetric, direct repeat arrangement of two motifs spaced by three nucleotides (DR3) provides an efficient interface of the DBDs of VDR and RXR (Fig. 1A, top). This fits with the so-called "3-4-5 rule" of Umesono et al. [20], in which VDR–RXR heterodimers show optimal binding to DR3-type REs, while other nuclear receptors, reflecting different structures and steric contraints, prefer altered spacing, such as DR4 for TRs and DR5 for RARs.

Genome-wide analyses for VDR binding sites (see Section 4) confirmed the preferential binding of VDR to DR3-type REs (Fig. 1A, bottom), but only for approximately one third of all genomic binding sites. Therefore, there must be additional mechanisms for how the VDR can associate with genomic loci, in order to

Download English Version:

https://daneshyari.com/en/article/10847704

Download Persian Version:

https://daneshyari.com/article/10847704

Daneshyari.com