Vitamin D (calciferol) metabolism

D'Eustachio, P., Holick, F., Huddart, R., Jassal, B., Matthews, L., May, B., Niskanen, E.
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 82

This document contains 1 pathway and 20 reactions (see Table of Contents)
Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-196791

Vitamin D3 (VD3, cholecalciferol) is a steroid hormone that principally plays roles in regulating intestinal calcium absorption and in bone metabolism. It is obtained from the diet and produced in the skin by photolysis of 7-dehydrocholesterol and released into the bloodstream. Very few foods (eg. oily fish, mushrooms exposed to sunlight and cod liver oil) are natural sources of vitamin D. A small number of countries in the world artificially fortify a few foods with vitamin D. The metabolites of vitamin D are carried in the circulation bound to a plasma protein called vitamin D binding protein (GC) (for review see Delanghe et al. 2015, Chun 2012). Vitamin D undergoes two subsequent hydroxylations to form the active form of the vitamin, 1-alpha, 25-dihydroxyvitamin D (1,25(OH)2D). The first hydroxylation takes place in the liver followed by subsequent transport to the kidney where the second hydroxylation takes place. 1,25(OH)2D acts by binding to nuclear vitamin D receptors (Neme et al. 2017) and it has been estimated that upwards of 2000 genes are directly or indirectly regulated which are involved in calcium homeostasis, immune responses, cellular growth, differentiation and apoptosis (Hossein-nezhad et al. 2013, Hossein-nezhad & Holick 2013). Inactivation of 1,25(OH)2D occurs via C23/C24 oxidation catalysed by cytochrome CYP24A1 enzyme (Christakos et al. 2016).

Literature references


Editions

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Photolytic cleavage and thermal isomerization of 7-dehydroCHOL

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-209754

Type: omitted

Compartments: endoplasmic reticulum membrane

Inferred from: Photolytic cleavage and thermal isomerization of 7-dehydrocholesterol (Rattus norvegicus)

The skin's exposure to UV rays from sunlight induces the photolytic cleavage of 7-dehydrocholesterol to previtamin D3. This is followed by thermal isomerization to form vitamin D3 (VD3, cholecalciferol) (Holick et al. 1977).

Followed by: VD3 translocates from ER membrane to extracellular region

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VD3 translocates from ER membrane to extracellular region

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-8963872

**Type:** uncertain

**Compartments:** endoplasmic reticulum membrane, extracellular region

Vitamin D metabolites such as VD3 are lipophilic and must be transported in the circulation bound to plasma proteins. VD3 translocates to the extracellular region where it binds GC, a vitamin D binding protein (Verboven et al. 2002).

**Preceded by:** Photolytic cleavage and thermal isomerization of 7-dehydroCHOL

**Followed by:** VD3 binds GC

**Literature references**


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VD3 binds GC

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-209738

**Type:** binding

**Compartments:** plasma membrane, extracellular region, cytosol

Vitamin D metabolites such as VD3 are lipophilic and must be transported in the circulation bound to plasma proteins. Vitamin D3 is transported to the liver bound to a plasma protein called vitamin D binding protein (GC aka DBP) (Verboven et al. 2002). GC is a 58 kDa circulating glycoprotein that transports vitamin D metabolites. The vast majority of vitamin D metabolites circulate bound to GC (85–90%), some bound to albumin (10–15%), with the remainder (<1%) circulating in the free form. GC has more than 1000-fold stronger binding affinity for vitamin D metabolites than albumin. Thus, the albumin-bound and free fractions of vitamin D metabolites are considered bioavailable (Denburg et al. 2016).

**Preceded by:** VD3 translocates from ER membrane to extracellular region

**Followed by:** VD3 dissociates from GC

**Literature references**


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**VD3 dissociates from GC**

- **Location:** Vitamin D (calciferol) metabolism
- **Stable identifier:** R-HSA-8963851
- **Type:** dissociation
- **Compartments:** extracellular region

Vitamin D3 (VD3) is transported to the liver bound to a plasma protein called vitamin D binding protein (GC aka DBP) (Verboven et al. 2002). Before uptake by the liver, VD3 must dissociate from GC.

- **Preceded by:** VD3 binds GC
- **Followed by:** VD3 translocates from extracellular region to ER membrane

**Literature references**


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VD3 translocates from extracellular region to ER membrane

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-350147

Type: transition

Compartments: endoplasmic reticulum membrane, extracellular region

Once vitamin D3 (VD3) is released from vitamin D binding protein (GC, DBP), it translocates from the extracellular region to the ER membrane, becoming available for hydroxylation by the microsomal enzyme CYP2R1 (Shinkyo et al. 2004).

Preceded by: VD3 dissociates from GC

Followed by: CYP2R1 25-hydroxylates VD3 to 25(OH)D

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**CYP2R1 25-hydroxylates VD3 to 25(OH)D**

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-209845

**Type:** transition

**Compartments:** endoplasmic reticulum membrane, cytosol

To be functionally active, vitamin D3 (VD3) needs to be dihydroxylated. The first hydroxylation at position 25 is carried out by ER membrane-located vitamin D 25-hydroxylase (CYP2R1) in the liver, forming 25-hydroxyvitamin D (calcidiol, 25(OH)D) (Shinkyo et al. 2004, Cheng et al. 2003).

**Preceded by:** VD3 translocates from extracellular region to ER membrane

**Followed by:** CYP27B1 hydroxylates 25(OH)D to 1,25(OH)2D, 25(OH)D translocates from ER membrane to extracellular region

**Literature references**


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25(OH)D translocates from ER membrane to extracellular region

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-6807242

**Type:** uncertain

**Compartments:** endoplasmic reticulum membrane, extracellular region

25-hydroxyvitamin D (calcidiol, 25(OH)D) translocates to the extracellular region (Verboven et al. 2002).

**Preceded by:** CYP2R1 25-hydroxylates VD3 to 25(OH)D

**Followed by:** 25(OH)D binds GC

**Literature references**


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25(OH)D binds GC

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-209944

Type: binding

Compartments: extracellular region

Vitamin D binding protein (GC aka DBP), a plasma protein, carries vitamin D metabolites in the circulation. 25-hydroxyvitamin D (25(OH)D) translocates to the extracellular region where it binds with GC and is transported to the kidney (Verboven et al. 2002).

Preceded by: 25(OH)D translocates from ER membrane to extracellular region

Followed by: CUBN binds GC:25(OH)D

Literature references


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CUBN binds GC:25(OH)D

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-350186

**Type:** binding

**Compartments:** plasma membrane, extracellular region

Cubilin (CUBN) is a membrane-associated protein colocalising with megalin (LRP2). Its function is to sequester steroid carrier complexes such as vitamin D binding protein:25-hydroxyvitamin D (GC:25(OH)D) on the cell surface before LRP2 mediates their internalisation (Nykjaer et al. 2001).

**Preceded by:** 25(OH)D binds GC

**Followed by:** LRP2-mediated uptake of extracellular CUBN:GC:25(OH)D

**Literature references**


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LRP2-mediated uptake of extracellular CUBN:GC:25(OH)D

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-350168

Type: omitted

Compartments: plasma membrane, extracellular region, cytosol

Megalin (LRP2, glycoprotein 330) is a member of the low density lipoprotein receptor family and is abundant in kidney proximal tubules (Kounnas et al. 1995, Hjalm et al. 1996). LRP2 complexed with LDLRAP1 (low density lipoprotein receptor adapter protein 1, aka ARH) mediates the endocytic uptake of GC:25(OH)D complexes, thereby preventing the loss of 25-hydroxyvitamin D (calcidiol, 25(OH)D) in urine (Nykjaer et al. 1999, Kaseda et al. 2011).

Preceded by: CUBN binds GC:25(OH)D

Followed by: Endocytic translocation of CUBN:GC:25(OH)D to lysosomal lumen

Literature references


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Endocytic translocation of CUBN:GC:25(OH)D to lysosomal lumen

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-209760

**Type:** omitted

**Compartments:** lysosomal lumen, cytosol

The internalized CUBN:GC:25(OH)D complex enters the lysosome where it can be acted upon the protease legumain (Halfon et al. 1998, Chen et al. 2000).

**Preceded by:** LRP2-mediated uptake of extracellular CUBN:GC:25(OH)D

**Followed by:** LGMN degrades GC

**Literature references**


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Mammalian legumain (LGMN, asparagine-specific endoprotease) is a subfamily of cysteine proteases with no homology to other known proteases and is found in a wide range of organisms from parasites to plants and animals. LGMN requires acidic conditions for its degradative activity. Cubilin (CUBN), once released from the complex, cycles back to the cell surface. Free 25-hydroxyvitamin D (calcidiol, 25(OH)D) becomes available for further processing (Nykjaer et al. 1999).

**Preceded by:** Endocytic translocation of CUBN:GC:25(OH)D to lysosomal lumen

**Followed by:** CUBN dissociates from 25(OH)D, 25(OH)D translocates from lysosomal lumen to cytosol

**Literature references**


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CUBN dissociates from 25(OH)D

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-8963864

**Type:** dissociation

**Compartments:** lysosomal lumen

Cubilin (CUBN), once released from the complex, cycles back to the cell surface. Free 25-hydroxyvitamin D (calcidiol, 25(OH)D) becomes available for further processing (Nykjaer et al. 1999).

**Preceded by:** LGMN degrades GC

**Literature references**


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25(OH)D translocates from lysosomal lumen to cytosol

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-209766

**Type:** uncertain

**Compartments:** lysosomal lumen, cytosol

Once out of the lysosome, 25-hydroxyvitamin D (calcidiol, 25(OH)D) translocates to the mitochondion where it is made available to the mitochondrial membrane-resident protein CYP27B1 for further hydroxylation. The mechanism of mitochondrial targeting is unknown but may involve some kind of intracellular vitamin D binding protein (IDBP). IDBPs are related to the hsc-70 family of heat shock proteins and may function to localise vitamin D metabolites to specific areas. No human IDBP has yet been characterised (Radons 2016).

**Preceded by:** LGMN degrades GC

**Followed by:** CYP27B1 hydroxylates 25(OH)D to 1,25(OH)2D

**Literature references**

CYP27B1 hydroxylates 25(OH)D to 1,25(OH)2D

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-209868

**Type:** transition

**Compartments:** cytosol, mitochondrial outer membrane


**Preceded by:** CYP2R1 25-hydroxylates VD3 to 25(OH)D, 25(OH)D translocates from lysosomal lumen to cytosol

**Followed by:** CYP24A1 hydroxylates 1,25(OH)2D, inactivating it, 1,25(OH)2D translocates from cytosol to nucleoplasm

**Literature references**


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CYP24A1 hydroxylates 1,25(OH)2D, inactivating it

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-209765

**Type:** transition

**Compartments:** mitochondrial inner membrane, cytosol

1-alpha, 25-dihydroxyvitamin D (1,25(OH)2D) is biologically inactivated through a series of reactions beginning with 24-hydroxylation and is most likely a mechanism of elimination. 24-Hydroxylation of vitamin D metabolites is largely regulated inversely to 1-hydroxylation, the initial step towards activation. Human cDNA encoding CYP24A1 was isolated in 1993 (Chen et al. 1993). Studies with expressed human CYP24A1 in Sf21 insect cells indicated that the enzyme could catalyze most, if not all, of the steps in the C23 and C24 oxidation pathways of 25(OH)D and 1,25(OH)2D metabolism (Beckman et al. 1996). Sakaki et al observed that the ratio of initial hydroxylation products at C24 to C23 was 4:1, indicating that the C24-oxidation pathway predominates in humans (Sakaki et al. 2000).

**Preceded by:** CYP27B1 hydroxylates 25(OH)D to 1,25(OH)2D

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The biologically active form of vitamin D, 1-alpha, 25-dihydroxyvitamin D (1,25(OH)2D), can be transported to any target tissue where it enters the nucleoplasm to interact with vitamin D receptor (VDR) to exert its effects. The mechanism of translocation from cytosol to nucleoplasm is unknown (see review for general description - Christakos et al. 2016).

**Preceded by:** CYP27B1 hydroxylates 25(OH)D to 1,25(OH)2D

**Followed by:** PIAS4 SUMOylates VDR with SUMO2, 1,25(OH)2D binds VDR

**Literature references**


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1,25(OH)2D binds VDR

**Location:** Vitamin D (calciferol) metabolism

**Stable identifier:** R-HSA-8963915

**Type:** binding

**Compartments:** nucleoplasm


**Preceded by:** 1,25(OH)2D translocates from cytosol to nucleoplasm

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PIAS4 SUMOylates VDR with SUMO2

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-4546387

Type: transition

Compartments: nucleoplasm

E3 SUMO-protein ligase (PIAS4) SUMOylates Vitamin D3 receptor (VDR) with SUMO2 (Jena et al. 2012). SUMOylation inhibits transcriptional activation by VDR in response to vitamin D.

Preceded by: 1,25(OH)2D translocates from cytosol to nucleoplasm

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The genomic mechanism of 1,25(OH)2D action involves the direct, high-affinity binding of 1,25(OH)2D-activated VDR/RXR to specific vitamin D response elements (VDREs) in and around target genes resulting in either activation or repression of transcription (Christakos et al. 2016). Vitamin D receptor (VDR) agonist drugs function in the same way as 1,25(OH)2D, resulting in activation of gene transcription. VDR agonist drugs bind VDR and activate transcription of genes involved in calcium and bone homeostasis and proliferation and differentiation. These drugs are used to treat secondary hyperparathyroidism (SHPT), bone diseases such as osteoporosis, psoriasis and alopecia.

Paricalcitol (trade name Zemplar) is a VDR agonist drug used for the prevention and treatment of secondary hyperparathyroidism, SHPT, causing excessive secretion of parathyroid hormone associated with chronic renal failure. It is an analog of 1,25-dihydroxyergocalciferol, the active form of vitamin D2 (ergocalciferol). However current evidence is not sufficient to demonstrate an advantage of paricalcitol over non-selective vitamin D derivatives for this indication (Cai et al. 2016, Xie et al. 2017). Doxercalciferol (trade name Hectorol) is a VDR agonist drug for secondary hyperparathyroidism and metabolic bone disease (Sprague & Ho 2002). It is a synthetic analog of ergocalciferol (vitamin D2). It suppresses parathyroid synthesis and secretion. Doxercalciferol needs a 25-hydroxylation step in the liver to become active and is independent of renal or extrarenal 1α-hydroxylase.

Eldecalcitol (trade name Edirol) is a VDR agonist drug used in Japan for the treatment of osteoporosis. Studies suggest Eldecalcitol reduces calcium reabsorption into the body from bones, therefore increasing bone mineral density, and increases calcium absorption in intestines (Matsumoto 2012, Noguchi et al. 2013). Calcipotriol (trade names Dovonex, Daivonex and Psorcutan) is a synthetic derivative of the active form of vitamin D, calcitriol. It is used in the long-term treatment of chronic plaque psoriasis (Salmhofer et al. 2000, Ito et al. 2016) and alopecia areata (Kim et al. 2012). Falecalcitriol (Ito et al. 2009) and maxacalcitol (Akizawa et al. 2015) are used to treat SHPT in Japan (Honda et al. 2014, Mizobuchi et al. 2017).

**Literature references**


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**Editions**

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