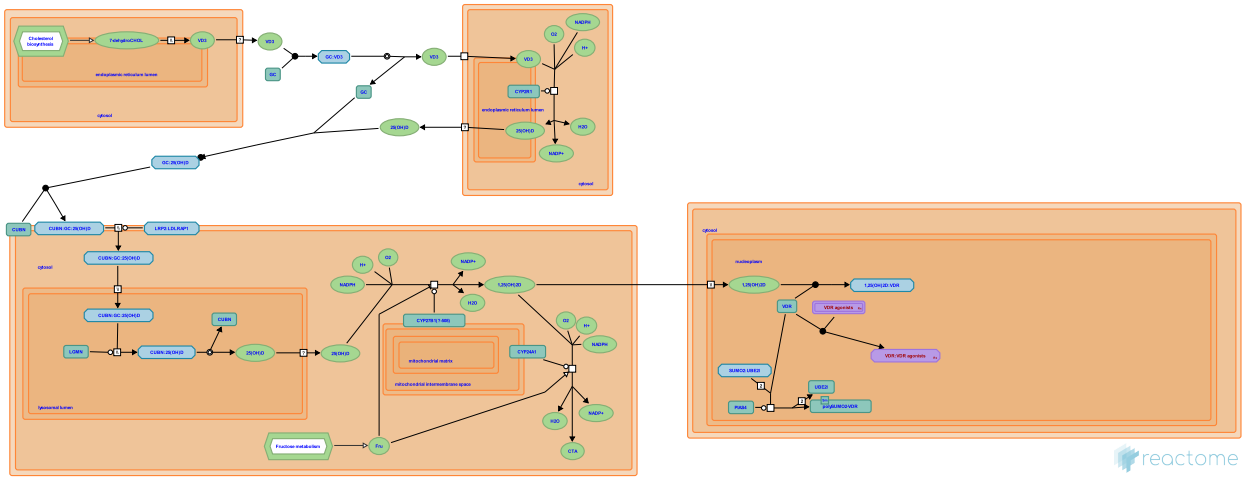
Vitamin D (calciferol) metabolism



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

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

27/04/2024

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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

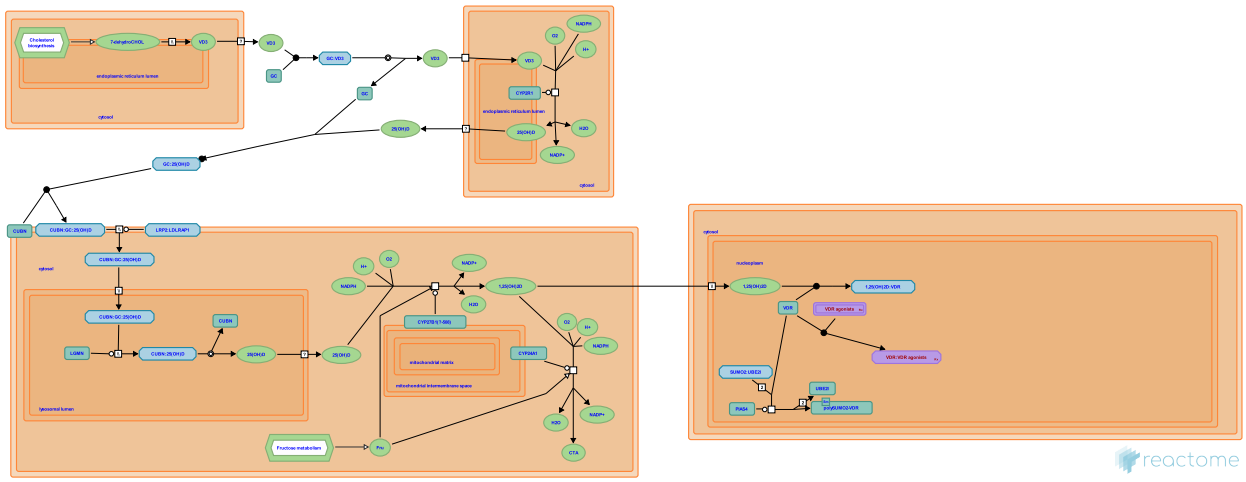
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

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

Carmeliet, G., Christakos, S., Dhawan, P., Verlinden, L., Verstuyf, A. (2016). Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. *Physiol. Rev., 96*, 365-408. ↗

Editions

2008-05-28	Reviewed	D'Eustachio, P.
2008-06-02	Edited	Jassal, B.
2008-10-01	Authored	Jassal, B.

Photolytic cleavage and thermal isomerization of 7-dehydroCHOL ↗

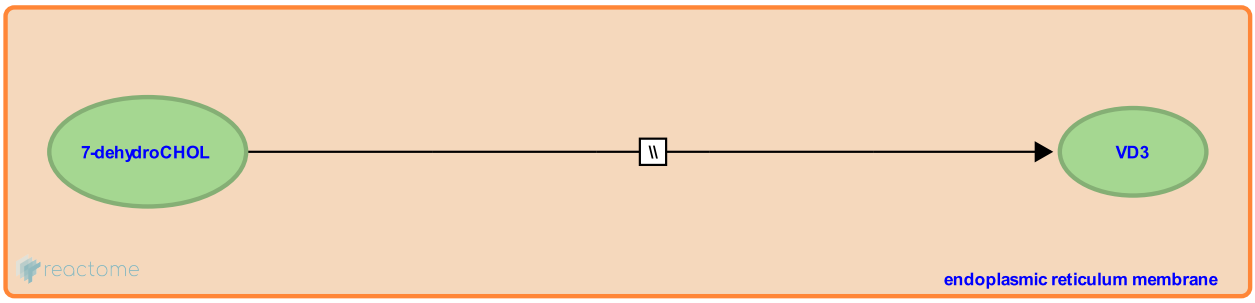
Location: Vitamin D (calciferol) metabolism

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

Editions

2008-05-28	Reviewed	D'Eustachio, P.
2008-06-02	Edited	Jassal, B.
2008-10-01	Authored	Jassal, B.

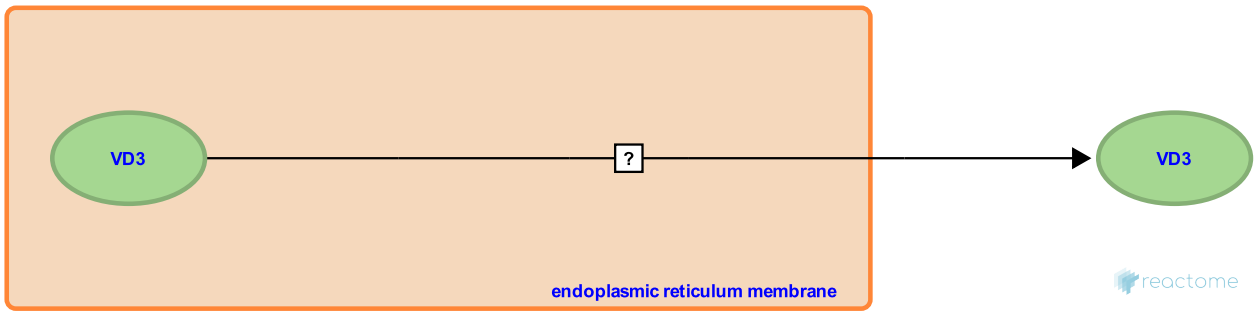
VD3 translocates from ER membrane to extracellular region ↗

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

De Maeyer, M., Bouillon, R., De Ranter, C., Van Baelen, H., Rabijns, A., Verboven, C. (2002). A structural basis for the unique binding features of the human vitamin D-binding protein. *Nat Struct Biol, 9*, 131-6. ↗

Editions

2008-05-28	Reviewed	D'Eustachio, P.
2017-02-13	Authored, Edited	Jassal, B.

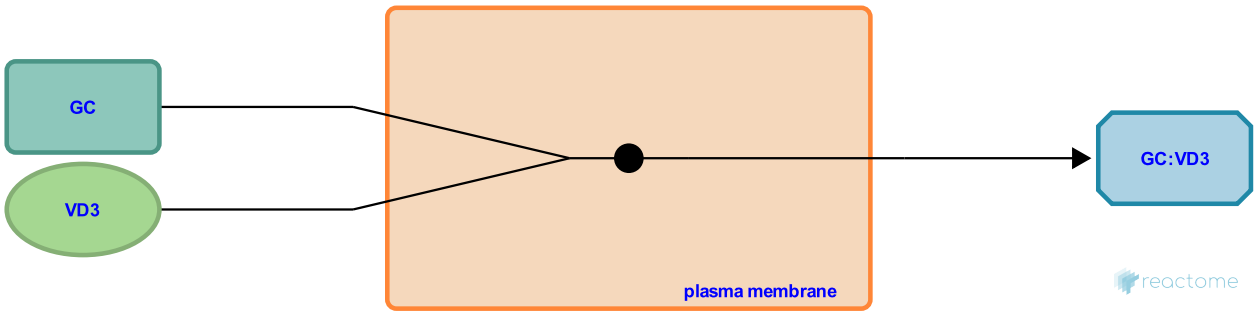
VD3 binds GC ↗

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

De Maeyer, M., Bouillon, R., De Ranter, C., Van Baelen, H., Rabijns, A., Verboven, C. (2002). A structural basis for the unique binding features of the human vitamin D-binding protein. *Nat Struct Biol, 9*, 131-6. ↗

Appel, LJ., Gupta, J., Sayed, S., Leonard, MB., de Boer, IH., Feldman, HI. et al. (2016). Comparison of Two ELISA Methods and Mass Spectrometry for Measurement of Vitamin D-Binding Protein: Implications for the Assessment of Bioavailable Vitamin D Concentrations Across Genotypes. *J. Bone Miner. Res., 31*, 1128-36. ↗

Editions

2008-05-28	Reviewed	D'Eustachio, P.
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2008-10-01	Authored	Jassal, B.
2017-06-14	Reviewed	D'Eustachio, P.

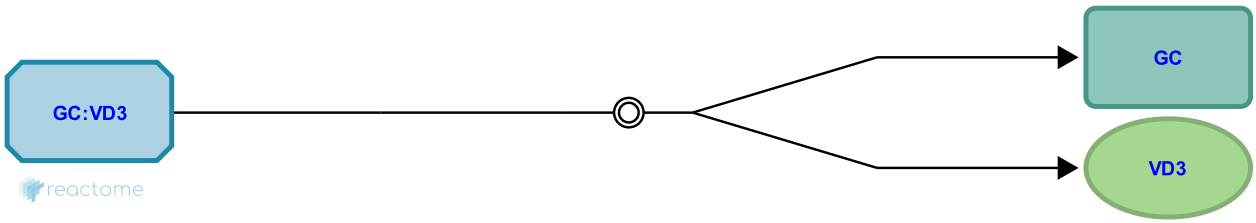
VD3 dissociates from GC ↗

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

De Maeyer, M., Bouillon, R., De Ranter, C., Van Baelen, H., Rabijns, A., Verboven, C. (2002). A structural basis for the unique binding features of the human vitamin D-binding protein. *Nat Struct Biol, 9*, 131-6. ↗

Editions

2017-02-13	Authored, Edited	Jassal, B.
2017-06-14	Reviewed	D'Eustachio, P.

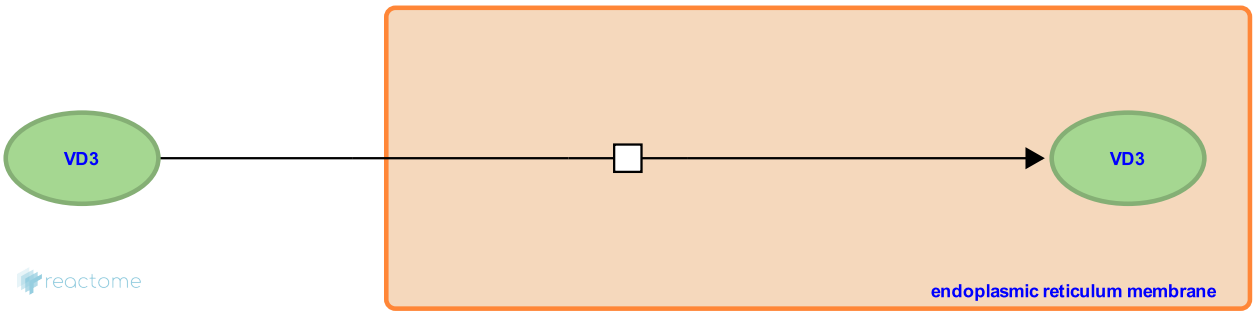
VD3 translocates from extracellular region to ER membrane ↗

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

Literature references

Shinkyo, R., Ohta, M., Sakaki, T., Kamakura, M., Inouye, K. (2004). Metabolism of vitamin D by human microsomal CYP2R1. *Biochem Biophys Res Commun, 324*, 451-7. ↗

Editions

2008-05-28	Reviewed	D'Eustachio, P.
2008-06-02	Edited	Jassal, B.
2008-10-01	Authored	Jassal, B.

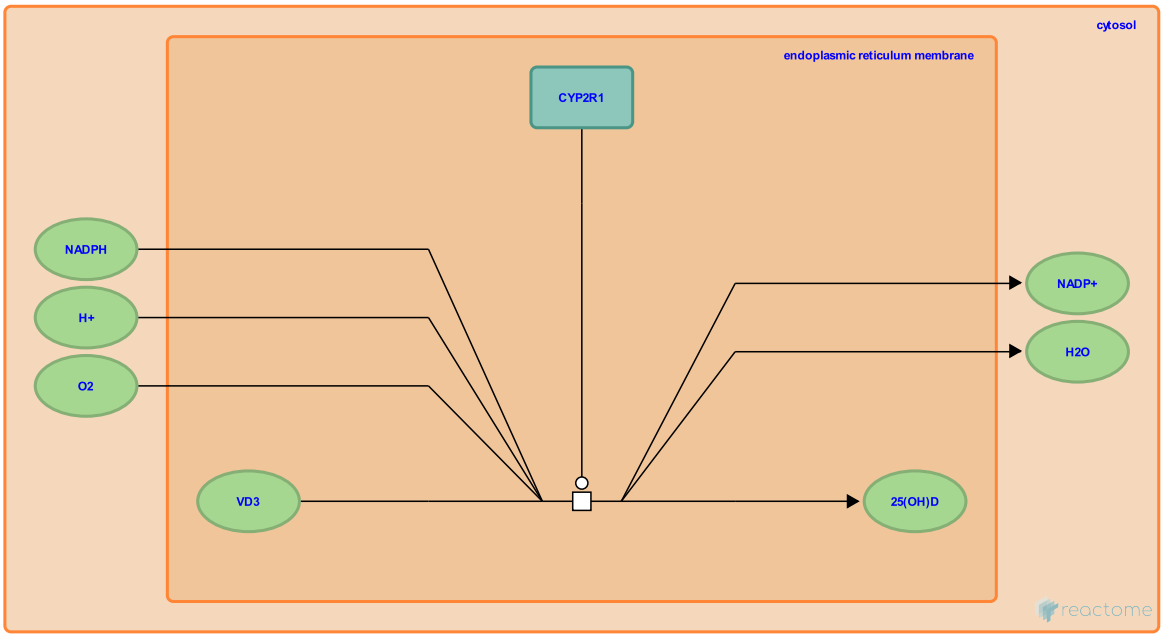
CYP2R1 25-hydroxylates VD3 to 25(OH)D ↗

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

Shinkyo, R., Ohta, M., Sakaki, T., Kamakura, M., Inouye, K. (2004). Metabolism of vitamin D by human microsomal CYP2R1. *Biochem Biophys Res Commun, 324*, 451-7. ↗

Mangelsdorf, DJ., Cheng, JB., Russell, DW., Motola, DL. (2003). De-orphanization of cytochrome P450 2R1: a microsomal vitamin D 25-hydroxilase. *J. Biol. Chem., 278*, 38084-93. ↗

Editions

2008-05-19	Edited	Jassal, B.
2008-05-28	Reviewed	D'Eustachio, P.
2008-05-28	Edited	Jassal, B.
2008-10-01	Authored	Jassal, B.

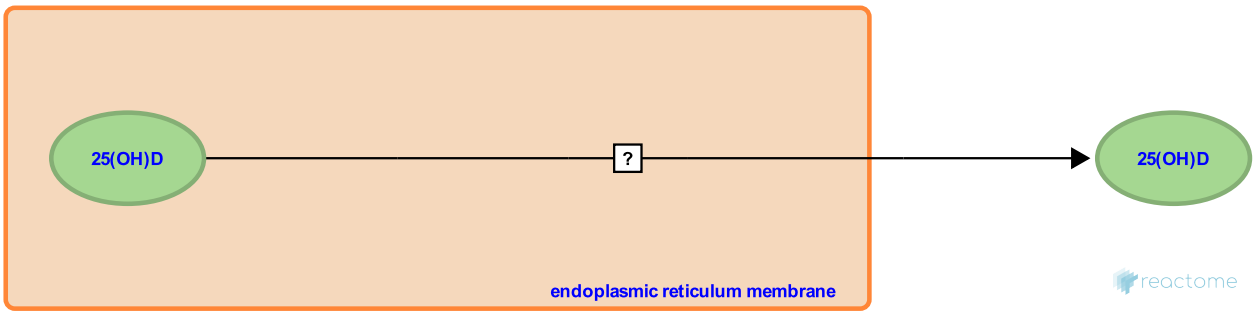
25(OH)D translocates from ER membrane to extracellular region ↗

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

De Maeyer, M., Bouillon, R., De Ranter, C., Van Baelen, H., Rabijns, A., Verboven, C. (2002). A structural basis for the unique binding features of the human vitamin D-binding protein. *Nat Struct Biol, 9*, 131-6. ↗

Editions

2015-10-30	Authored, Edited	Jassal, B.
2015-11-02	Reviewed	D'Eustachio, P.

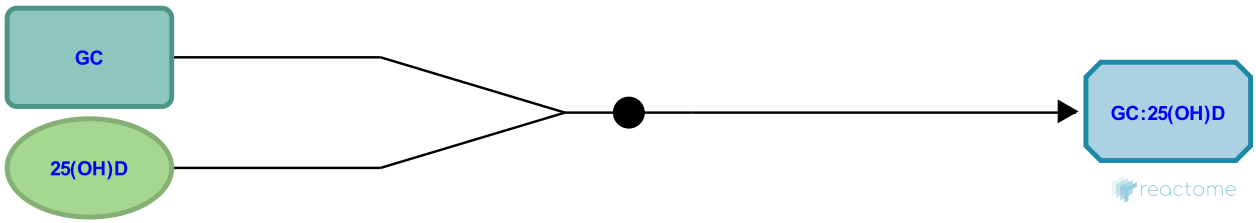
25(OH)D binds GC ↗

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

De Maeyer, M., Bouillon, R., De Ranter, C., Van Baelen, H., Rabijns, A., Verboven, C. (2002). A structural basis for the unique binding features of the human vitamin D-binding protein. *Nat Struct Biol, 9*, 131-6. ↗

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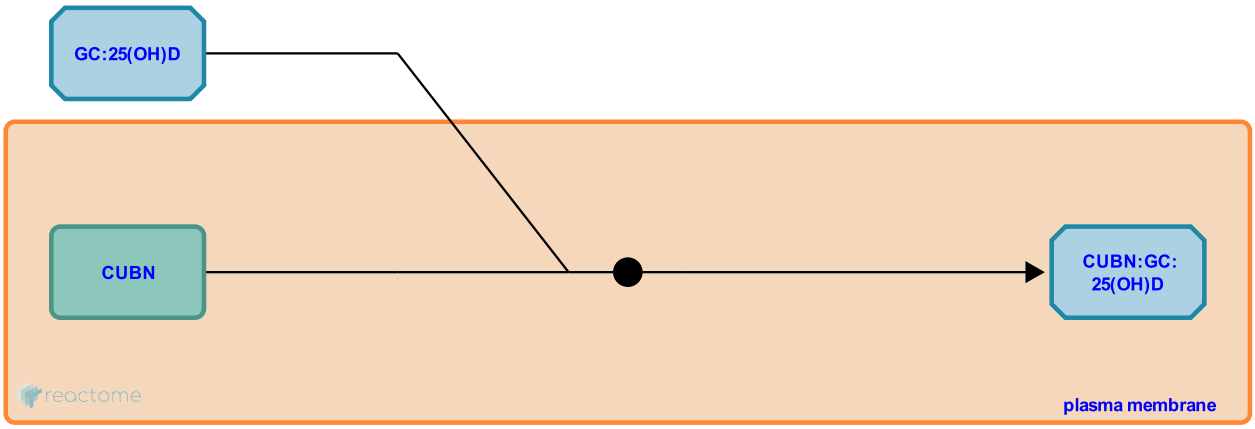
CUBN binds GC:25(OH)D ↗

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

Fyfe, JC., Gliemann, J., Jacobsen, C., Leheste, JR., Nielsen, MS., Willnow, TE. et al. (2001). Cubilin dysfunction causes abnormal metabolism of the steroid hormone 25(OH) vitamin D(3). *Proc Natl Acad Sci U S A, 98*, 13895-900. ↗

Editions

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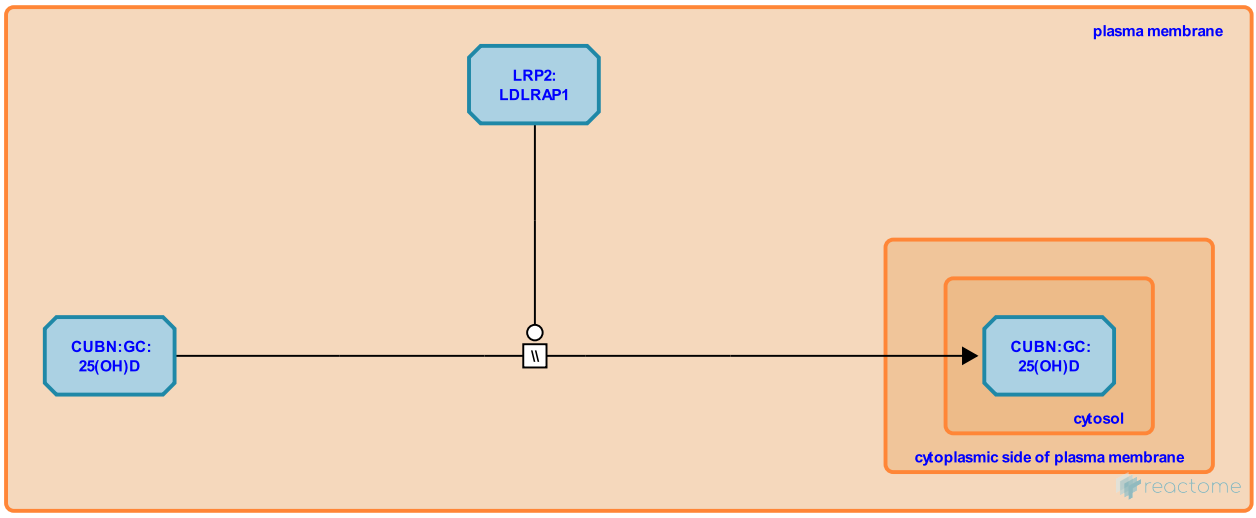
LRP2-mediated uptake of extracellular CUBN:GC:25(OH)D ↗

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

Hosojima, M., Sato, H., Kaseda, R., Saito, A. (2011). Role of megalin and cubilin in the metabolism of vitamin D(3). *Ther Apher Dial, 15*, 14-7. ↗

Melsen, F., Christensen, EI., Jacobsen, C., Vorum, H., Nykjaer, A., Willnow, TE. et al. (1999). An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. *Cell, 96*, 507-15. ↗

Brewer, BH., Stefansson, S., Harmony, JA., Loukinova, EB., Kounnas, MZ., Strickland, DK. et al. (1995). Identification of glycoprotein 330 as an endocytic receptor for apolipoprotein J/clusterin. *J Biol Chem, 270*, 13070-5. ↗

Lundgren, S., Murray, E., Larsson, M., Crumley, G., Hellman, P., Akerstrom, G. et al. (1996). Cloning and sequencing of human gp330, a Ca(2+)-binding receptor with potential intracellular signaling properties. *Eur J Biochem, 239*, 132-7. ↗

Editions

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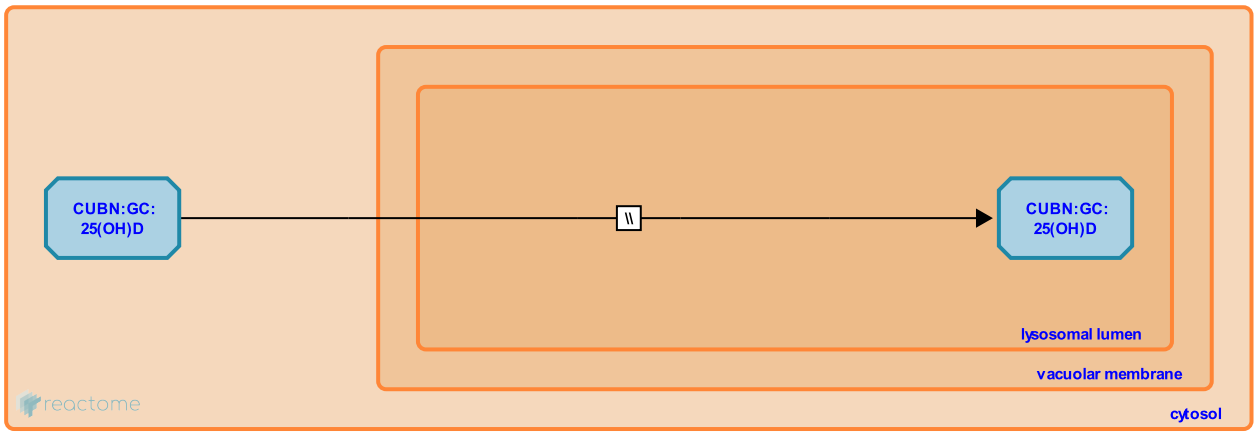
Endocytic translocation of CUBN:GC:25(OH)D to lysosomal lumen ↗

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

Zurawski, S., Halfon, S., Zurawski, G., Vega, F., Patel, S. (1998). Autocatalytic activation of human legumain at aspartic acid residues. *FEBS Lett, 438*, 114-8. ↗

Barrett, AJ., Chen, JM., Fortunato, M. (2000). Activation of human prolegumain by cleavage at a C-terminal asparagine residue. *Biochem J, 352*, 327-34. ↗

Editions

2008-05-28	Reviewed	D'Eustachio, P.
2008-06-02	Edited	Jassal, B.
2008-10-01	Authored	Jassal, B.

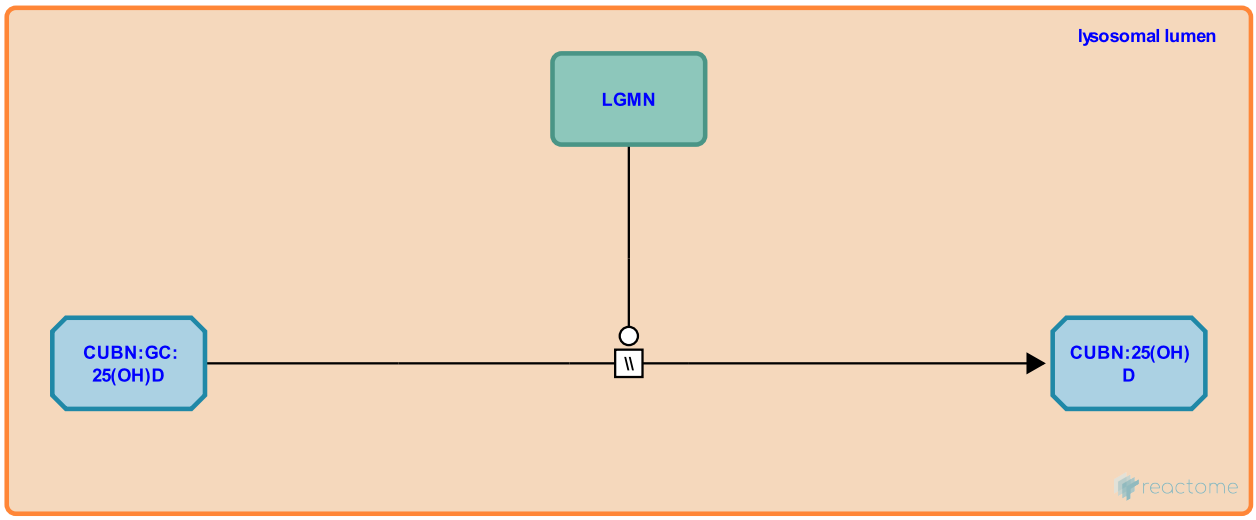
LGMN degrades GC ↗

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-350158

Type: omitted

Compartments: lysosomal lumen



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

Melsen, F., Christensen, EI., Jacobsen, C., Vorum, H., Nykjaer, A., Willnow, TE. et al. (1999). An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. *Cell, 96*, 507-15. ↗

Editions

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2008-10-01	Authored	Jassal, B.

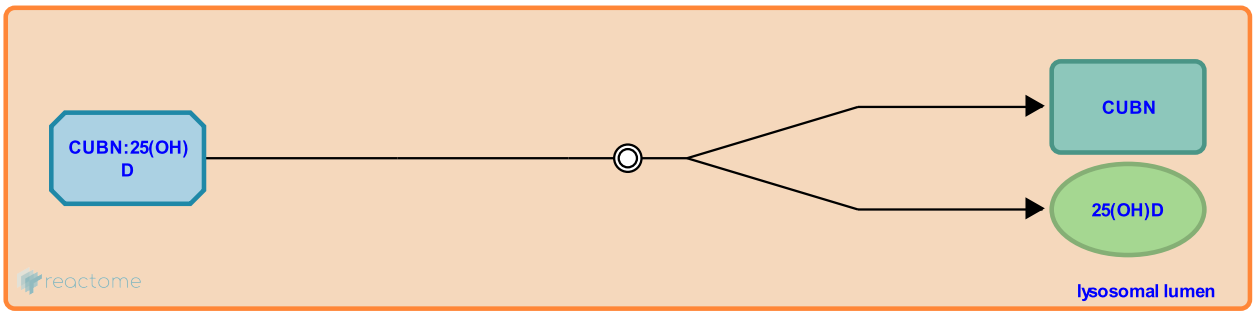
CUBN dissociates from 25(OH)D ↗

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

Melsen, F., Christensen, EI., Jacobsen, C., Vorum, H., Nykjaer, A., Willnow, TE. et al. (1999). An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. *Cell, 96*, 507-15. ↗

Editions

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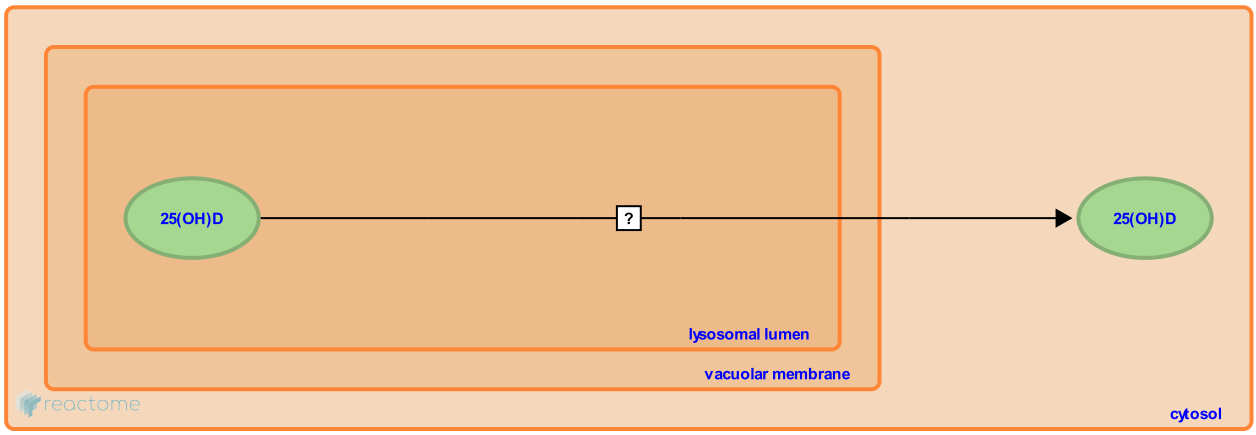
25(OH)D translocates from lysosomal lumen to cytosol ↗

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

Radons, J. (2016). The human HSP70 family of chaperones: where do we stand?. *Cell Stress Chaperones, 21*, 379-404. ↗

Editions

2008-05-28	Reviewed	D'Eustachio, P.
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2008-10-01	Authored	Jassal, B.

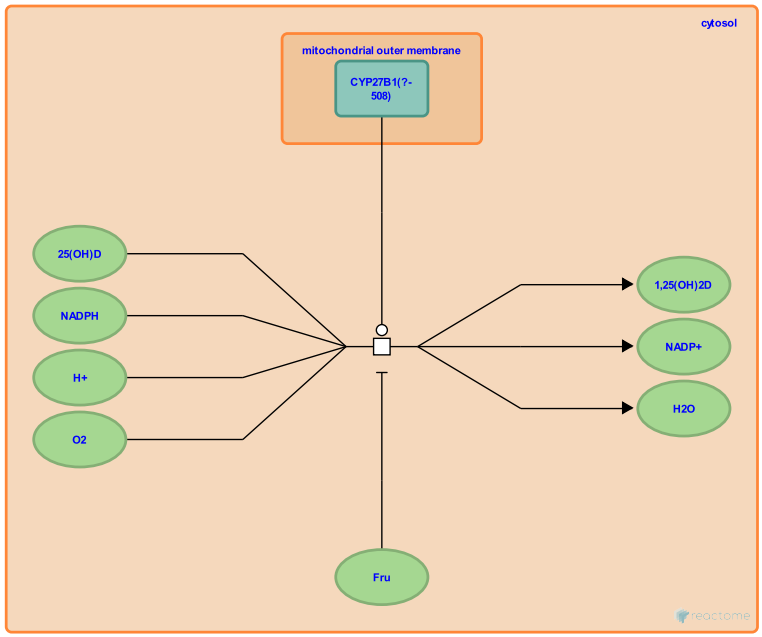
CYP27B1 hydroxylates 25(OH)D to 1,25(OH)2D ↗

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-209868

Type: transition

Compartments: cytosol, mitochondrial outer membrane



The second step in vitamin D activation requires hydroxylation of 25-hydroxyvitamin D (calcidiol, 25(OH)D) to 1-alpha, 25-dihydroxyvitamin D (1,25(OH)2D). This conversion is mediated by 25-hydroxyvitamin D-1-alpha hydroxylase (CYP27B1), an outer mitochondrial membrane-resident protein (Zehnder et al. 2002, Fritsche et al. 2003, Sawada et al. 1999).

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

Zehnder, D., Stewart, PM., Howie, AJ., Bland, R., Wheeler, DC., Hewison, M. et al. (2002). Synthesis of 1,25-dihydroxyvitamin D(3) by human endothelial cells is regulated by inflammatory cytokines: a novel autocrine determinant of vascular cell adhesion. *J Am Soc Nephrol, 13*, 621-9. ↗

Kreutz, M., Andreesen, R., Mondal, K., Fritsche, J., Ehrnsperger, A. (2003). Regulation of 25-hydroxyvitamin D3-1 alpha-hydroxylase and production of 1 alpha,25-dihydroxyvitamin D3 by human dendritic cells. *Blood, 102*, 3314-6. ↗

Kato, S., Sakaki, T., Sawada, N., Inouye, K., Takeyama, K., Kitanaka, S. (1999). Enzymatic properties of human 25-hydroxyvitamin D3 1alpha-hydroxylase coexpression with adrenodoxin and NADPH-adrenodoxin reductase in Escherichia coli. *Eur. J. Biochem., 265*, 950-6. ↗

Editions

2008-05-19	Edited	Jassal, B.
2008-05-28	Reviewed	D'Eustachio, P.
2008-10-01	Authored	Jassal, B.
2014-06-23	Revised	Jassal, B.

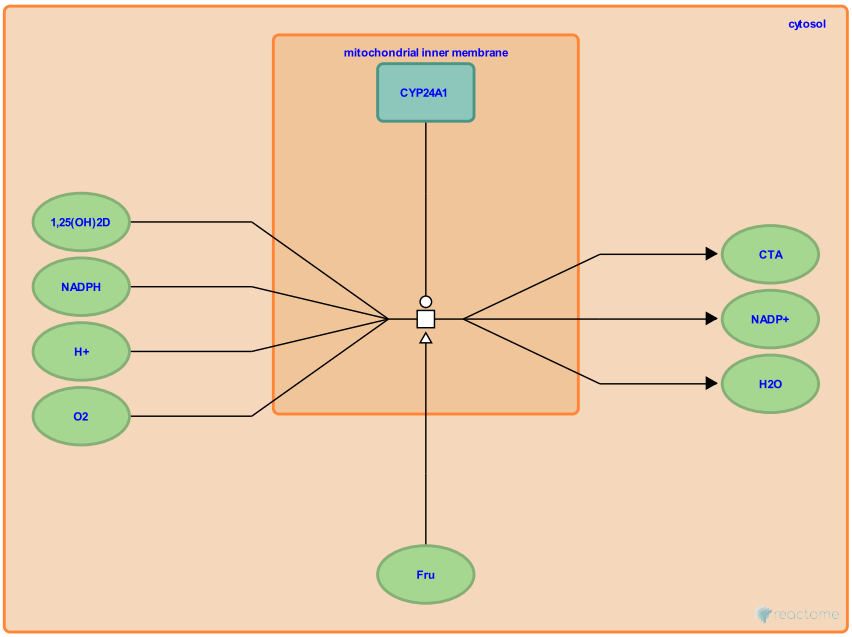
CYP24A1 hydroxylates 1,25(OH)2D, inactivating it ↗

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

Literature references

Beckman, MJ., DeLuca, HF., Yamada, S., Prahl, J., Tadikonda, P., Werner, E. (1996). Human 25-hydroxyvitamin D3-24-hydroxylase, a multicatalytic enzyme. *Biochemistry, 35*, 8465-72. ↗

Prahl, JM., Chen, KS., DeLuca, HF. (1993). Isolation and expression of human 1,25-dihydroxyvitamin D3 24-hydroxylase cDNA. *Proc Natl Acad Sci U S A, 90*, 4543-7. ↗

Komai, K., Sawada, N., Ohyama, Y., Shiozawa, S., Sakaki, T., Yamada, S. et al. (2000). Dual metabolic pathway of 25-hydroxyvitamin D3 catalyzed by human CYP24. *Eur J Biochem, 267*, 6158-65. ↗

Editions

2008-05-28	Reviewed	D'Eustachio, P.
2008-06-02	Edited	Jassal, B.
2008-10-01	Authored	Jassal, B.

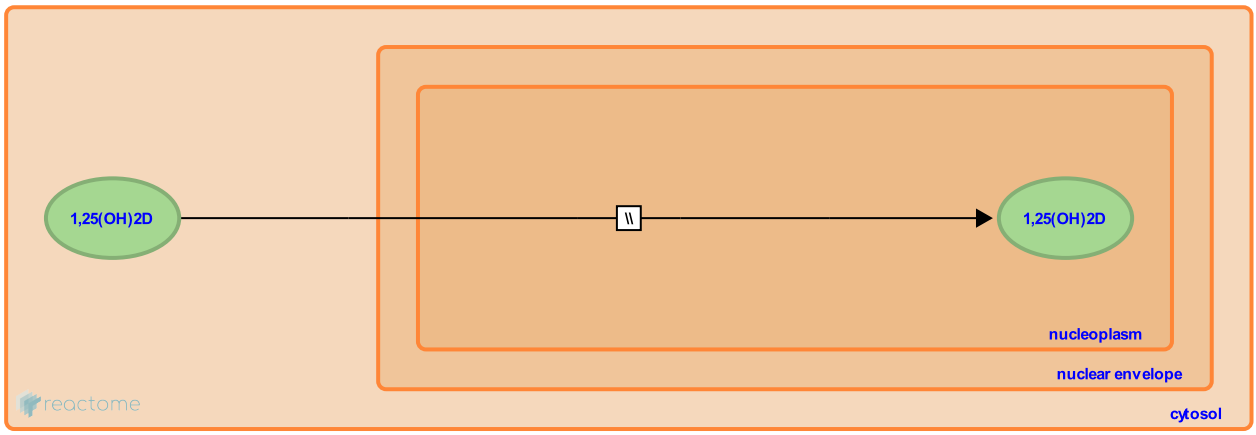
1,25(OH)2D translocates from cytosol to nucleoplasm

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-8963913

Type: omitted

Compartments: nucleoplasm, cytosol



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

Carmeliet, G., Christakos, S., Dhawan, P., Verlinden, L., Verstuyf, A. (2016). Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. *Physiol. Rev., 96*, 365-408.

Editions

2017-02-14	Authored, Edited	Jassal, B.
2017-11-09	Reviewed	Holick, F.

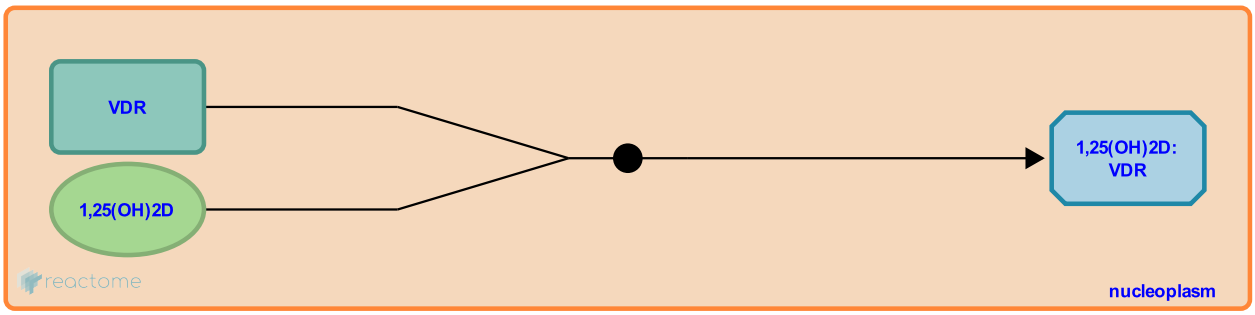
1,25(OH)2D binds VDR ↗

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-8963915

Type: binding

Compartments: nucleoplasm



The biologically active form of vitamin D, 1-alpha, 25-dihydroxyvitamin D (1,25(OH)2D), interacts with the nuclear hormone receptor vitamin D receptor (VDR) in the nucleoplasm of any target tissue (Neme et al. 2017). VDR regulates the actions of 1,25(OH)2D and their binding recruits coactivators (Eelen et al. 2005, Kim et al. 2005, Du et al. 2017) to initiate a signaling response that regulates an estimated upwards of 2000 genes involved in calcium homeostasis, immune responses, cellular growth, differentiation and apoptosis (Hossein-nezhad et al. 2013, Hossein-nezhad & Holick 2013, Wolden-Kirk et al. 2012, Prietl et al. 2013, Hewison 2012, Christakos et al. 2016, Bandera Merchan et al. 2017).

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

Literature references

Hewison, M. (2012). Vitamin D and immune function: an overview. *Proc Nutr Soc, 71*, 50-61. ↗

Moras, D., Vandewalle, M., Rochel, N., Tocchini-Valentini, G., Claessens, F., Verstuyf, A. et al. (2005). Superagonistic action of 14-epi-analogs of 1,25-dihydroxyvitamin D explained by vitamin D receptor-coactivator interaction. *Mol. Pharmacol., 67*, 1566-73. ↗

Amrein, K., Pieber, TR., Prietl, B., Treiber, G. (2013). Vitamin D and immune function. *Nutrients, 5*, 2502-21. ↗

Du, C., Yang, S., Dong, H., Zhao, X. (2017). Pathogenic roles of alterations in vitamin D and vitamin D receptor in gastric tumorigenesis. *Oncotarget, 8*, 29474-29486. ↗

Mathieu, C., Verstuyf, A., Gysemans, C., Wolden-Kirk, H. (2012). Extraskeletal effects of vitamin D. *Endocrinol. Metab. Clin. North Am., 41*, 571-94. ↗

Editions

2017-02-14	Authored, Edited	Jassal, B.
2017-11-09	Reviewed	Holick, F.

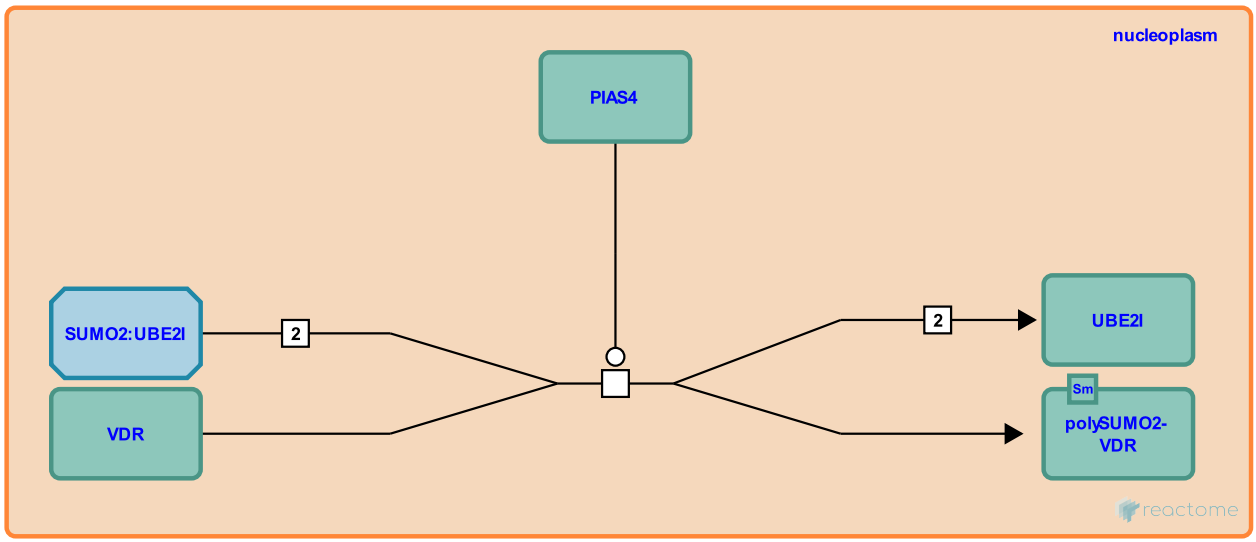
PIAS4 SUMOylates VDR with SUMO2 ↗

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

Literature references

Lee, WP., Thompson, PD., Doherty, D., Jena, S. (2012). PIAS4 represses vitamin D receptor-mediated signaling and acts as an E3-SUMO ligase towards vitamin D receptor. *J. Steroid Biochem. Mol. Biol., 132*, 24-31. ↗

Editions

2013-08-19	Authored, Edited	May, B.
2018-05-09	Reviewed	Niskanen, E.
2018-08-08	Reviewed	Niskanen, E.

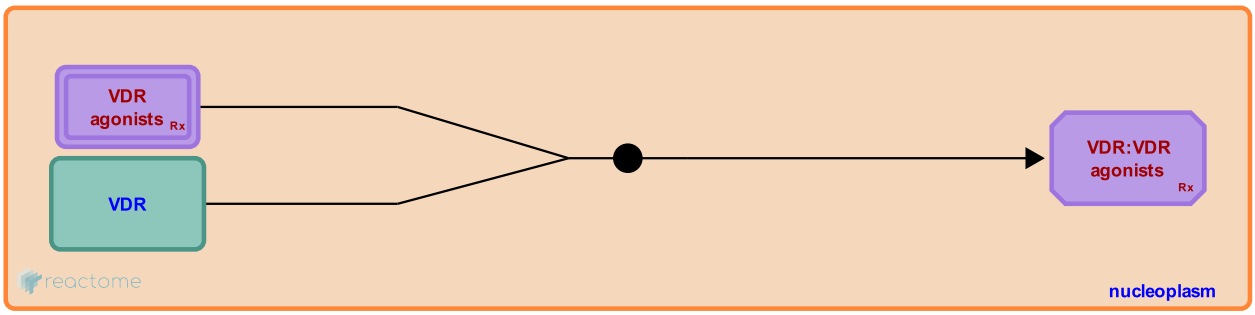
VDR agonists bind VDR ↗

Location: Vitamin D (calciferol) metabolism

Stable identifier: R-HSA-9660192

Type: binding

Compartments: nucleoplasm



The genomic mechanism of 1,25(OH)2D action involves the direct, high-affinity binding of 1,25(OH)2D-activated VDR/RXRA 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

Cai, P., Li, Z., Ji, L., Tang, X., Qin, W. (2016). Comparison between paricalcitol and active non-selective vitamin D receptor activator for secondary hyperparathyroidism in chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials. *Int Urol Nephrol, 48*, 571-84. ↗

Koiwa, F., Suzuki, R., Takahashi, K., Michihata, T., Shishido, K., Sekiguchi, T. et al. (2014). Active vitamin D analogs, maxacalcitol and alfacalcidol, as maintenance therapy for mild secondary hyperparathyroidism in hemodialysis patients - a randomized study. *Int J Clin Pharmacol Ther, 52*, 360-8. ↗

Koiwa, F., Akizawa, T., Ogata, H., Kinugasa, E., Mizobuchi, M. (2017). Research on kidney and mineral metabolism in Japan: past, present, and future. *Clin. Exp. Nephrol., 21*, 4-8. ↗

Matsumoto, T. (2012). Osteoporosis treatment by a new active vitamin D3 compound, eldecalcitol, in Japan. *Curr Osteoporos Rep, 10*, 248-50. ↗

Kim, HM., Choi, SY., Lee, JW., Kim, DH., Kim, BJ., Kim, MN. et al. (2012). Successful treatment of alopecia areata with topical calcipotriol. *Ann Dermatol, 24*, 341-4. ↗

Editions

2021-03-25	Authored	Jassal, B.
2021-10-27	Edited	Jassal, B.
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