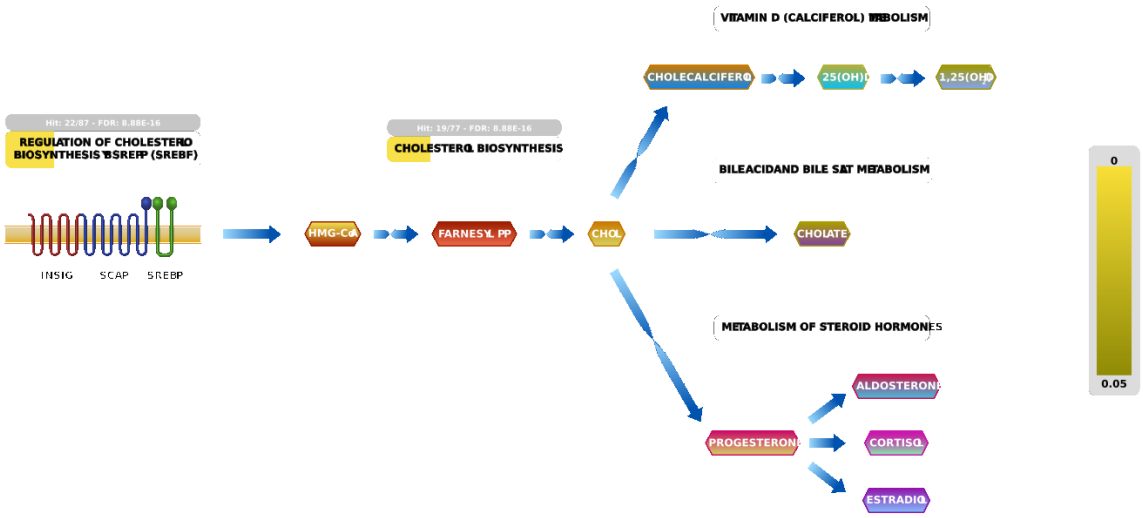
Metabolism of steroids



D'Eustachio, P., Jassal, B., Liang, G., May, B., Rozman, D J.

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

15/05/2022

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. ↗

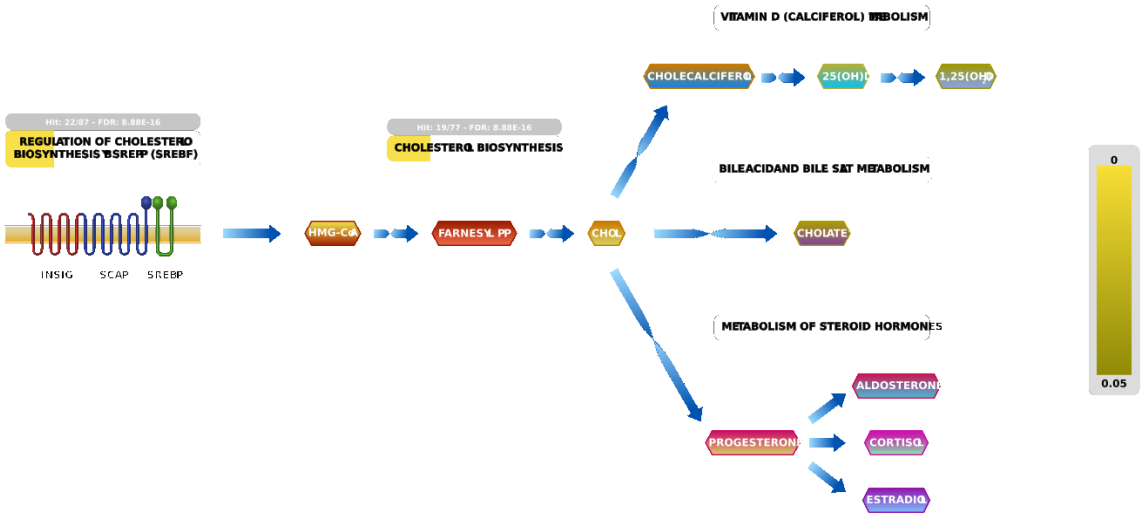
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Analysis properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method. See more
- 18 out of 21 identifiers in the sample were found in Reactome, where 41 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMjA1MTQxNTM0MzNfNDkyOA%3D%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

Metabolism of steroids ↗

Stable identifier: R-HSA-8957322



Steroids, defined by a four-ring cyclopenta[a]phenanthrene carbon skeleton, include cholesterol and bile acids and salts, steroid hormones, and vitamin D, three groups of molecules synthesized from it. In this module, pathways for the synthesis of cholesterol from HMG-CoA (hydroxymethylglutaryl-coenzyme A) (Russell 1992), and for its conversion to bile acids and salts (Russell 2003), steroid hormones (Payne & Hales 2004), and vitamin D (Dusso et al. 2005) are annotated, together with the SREBP-mediated regulatory process that normally links the rate of cholesterol synthesis to levels of cellular cholesterol (Brown & Goldstein 2009).

Literature references

Slatopolsky, E., Brown, AJ., Dusso, AS. (2005). Vitamin D. *Am J Physiol Renal Physiol, 289*, F8-28. ↗

Brown, MS., Goldstein, JL. (2009). Cholesterol feedback: from Schoenheimer's bottle to Scap's MELADL. *J Lipid Res, 50*, S15-27. ↗

Russell, DW. (1992). Cholesterol biosynthesis and metabolism. *Cardiovasc Drugs Ther, 6*, 103-10. ↗

Payne, AH., Hales, DB. (2004). Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. *Endocr Rev, 25*, 947-70. ↗

Russell, DW. (2003). The enzymes, regulation, and genetics of bile acid synthesis. *Annu Rev Biochem, 72*, 137-74. ↗

Editions

2007-01-24	Authored, Edited	Jassal, B.
2015-11-02	Reviewed	Jassal, B.

18 submitted entities found in this pathway, mapping to 32 Reactome entities

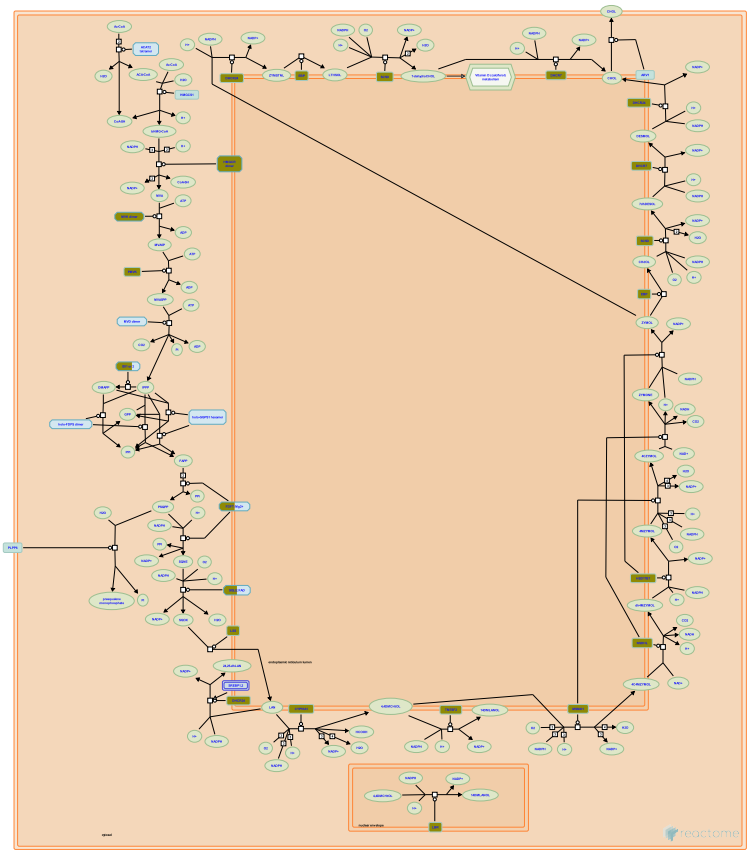
Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CYP51A1	Q16850	DHCR24	Q15392	DHCR7	Q9UBM7
EBP	Q15125	FDFT1	P37268	HMGCR	P04035-1, P04035-2
HSD17B7	P56937	IDI1	Q13907	IDI2	Q13907, Q9BXS1
LBR	O76062, Q14739	LSS	P48449	MSMO1	Q15800
MVK	Q03426	NSDHL	Q15738	PMVK	Q15126
SC5D	O75845	SQLE	Q14534	TM7SF2	O76062

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
CYP51A1	ENSG00000001630	DHCR7	ENSG00000172893	FDFT1	ENSG00000079459
HMGCR	ENSG00000113161	IDI1	ENSG00000067064	LSS	ENSG00000160285
MVK	ENSG00000110921	PMVK	ENSG00000163344	SC5D	ENSG00000109929
SQLE	ENSG00000104549	TM7SF2	ENSG00000149809		

Cholesterol biosynthesis ↗

Location: Metabolism of steroids

Stable identifier: R-HSA-191273



Cholesterol is synthesized de novo from acetyl CoA. The overall synthetic process is outlined in the attached illustration. Enzymes whose regulation plays a major role in determining the rate of cholesterol synthesis in the body are highlighted in red, and connections to other metabolic processes are indicated. The transformation of zymosterol into cholesterol can follow either of routes, one in which reduction of the double bond in the isooctyl side chain is the final step (cholesterol synthesis via desmosterol, also known as the Bloch pathway) and one in which this reduction is the first step (cholesterol biosynthesis via lathosterol, also known as the Kandutsch-Russell pathway). The former pathway is prominent in the liver and many other tissues while the latter is prominent in skin, where it may serve as the source of the 7-dehydrocholesterol that is the starting point for the synthesis of D vitamins. Defects in several of the enzymes involved in this process are associated with human disease and have provided useful insights into the regulatory roles of cholesterol and its synthetic intermediates in human development (Gaylor 2002; Herman 2003; Kandutsch & Russell 1960; Mitsche et al. 2015; Song et al. 2005).

Literature references

Rudney, H., Sexton, RC. (1986). Regulation of cholesterol biosynthesis. *Annu Rev Nutr, 6*, 245-72. ↗

Russell, DW. (1992). Cholesterol biosynthesis and metabolism. *Cardiovasc Drugs Ther, 6*, 103-10. ↗

Herman, GE. (2003). Disorders of cholesterol biosynthesis: prototypic metabolic malformation syndromes. *Hum Mol Genet, 12*, R75-88. ↗

Gaylor, JL. (2002). Membrane-bound enzymes of cholesterol synthesis from lanosterol. *Biochem Biophys Res Commun, 292*, 1139-46. ↗

Song, BL., DeBose-Boyd, RA., Javitt, NB. (2005). Insig-mediated degradation of HMG CoA reductase stimulated by lanosterol, an intermediate in the synthesis of cholesterol. *Cell Metab, 1*, 179-89. ↗

Editions

2007-01-22	Edited, Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.
2015-11-02	Revised	D'Eustachio, P.
2015-11-02	Reviewed	Jassal, B.
2021-11-23	Revised	Rozman, D J.

18 submitted entities found in this pathway, mapping to 21 Reactome entities

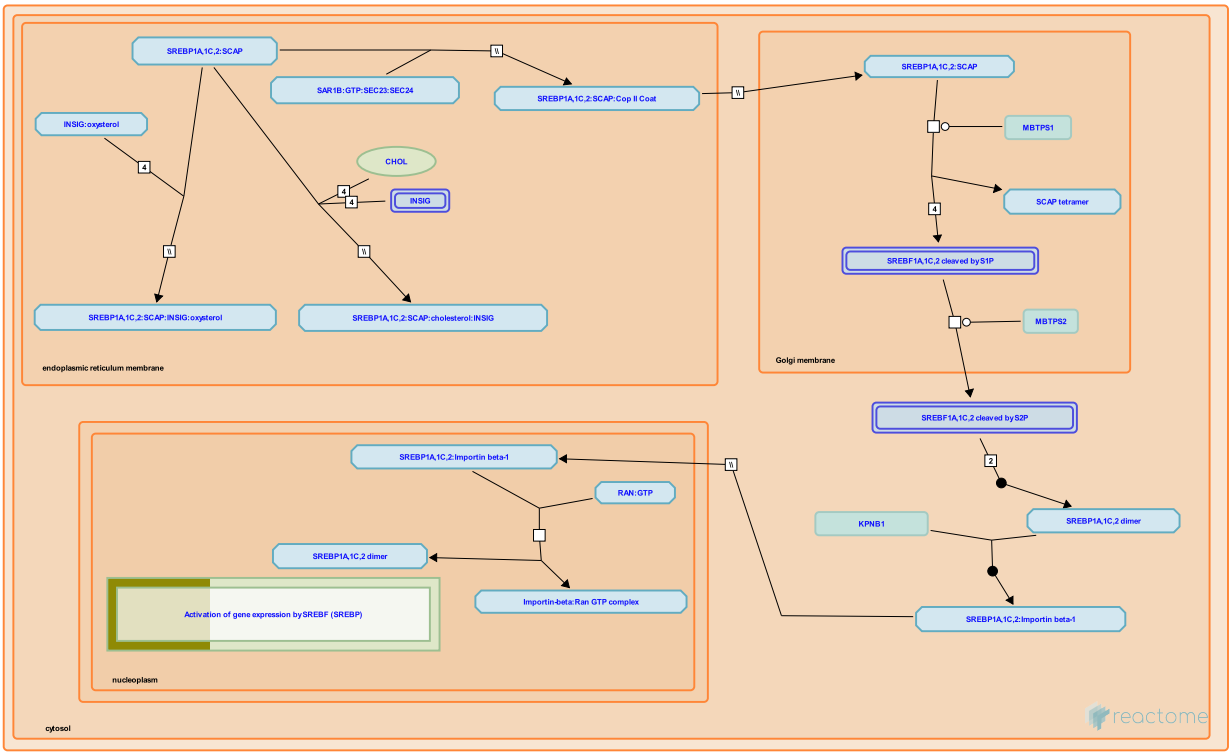
Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CYP51A1	Q16850	DHCR24	Q15392	DHCR7	Q9UBM7
EBP	Q15125	FDFT1	P37268	HMGCR	P04035-1, P04035-2
HSD17B7	P56937	IDI1	Q13907	IDI2	Q13907, Q9BXS1
LBR	O76062, Q14739	LSS	P48449	MSMO1	Q15800
MVK	Q03426	NSDHL	Q15738	PMVK	Q15126
SC5D	O75845	SQLE	Q14534	TM7SF2	O76062

Regulation of cholesterol biosynthesis by SREBP (SREBF) ↗

Location: Metabolism of steroids

Stable identifier: R-HSA-1655829

Compartments: endoplasmic reticulum membrane, nucleoplasm, Golgi membrane, ER to Golgi transport vesicle membrane



Sterol regulatory element binding proteins (SREBPs, SREBFs) respond to low cholesterol concentrations by transiting to the nucleus and activating genes involved in cholesterol and lipid biosynthesis (reviewed in Brown and Goldstein 2009, Osborne and Espenshade 2009, Weber et al. 2004).

Newly synthesized SREBPs are transmembrane proteins that bind SCAP in the endoplasmic reticulum (ER) membrane. SCAP binds cholesterol which causes a conformational change that allows SCAP to interact with INSIG, retaining the SCAP:SREBP complex in the ER. INSIG binds oxysterols, which cause INSIG to bind SCAP and retain SCAP:SREBP in the endoplasmic reticulum.

In low cholesterol (below about 5 mol%) SCAP no longer interacts with cholesterol or INSIG and binds Sec24 of the CopII coat complex instead. Thus SCAP:SREBP transits with the CopII complex from the ER to the Golgi. In the Golgi SREBP is cleaved by S1P and then by S2P, releasing the N-terminal fragment of SREBP into the cytosol. The N-terminal fragment is imported to the nucleus by importin-beta and then acts with other factors, such as SP1 and NF-Y, to activate transcription of target genes. Targets of SREBP include the genes encoding all enzymes of cholesterol biosynthesis and several genes involved in lipogenesis. SREBP2 most strongly activates cholesterol biosynthesis while SREBP1C most strongly activates lipogenesis.

Literature references

Brown, MS., Goldstein, JL. (2009). Cholesterol feedback: from Schoenheimer's bottle to Scap's MELADL. *J Lipid Res, 50*, S15-27. ↗

Osborne, TF., Espenshade, PJ. (2009). Evolutionary conservation and adaptation in the mechanism that regulates SREBP action: what a long, strange tRIP it's been. *Genes Dev, 23*, 2578-91. ↗

Stampfl, A., Boll, M., Weber, LW. (2004). Maintaining cholesterol homeostasis: sterol regulatory element-binding proteins. *World J Gastroenterol, 10*, 3081-7. ↗

Editions

2011-09-28	Authored	May, B.
2011-10-13	Edited	May, B.
2012-08-25	Reviewed	Liang, G.

13 submitted entities found in this pathway, mapping to 24 Reactome entities

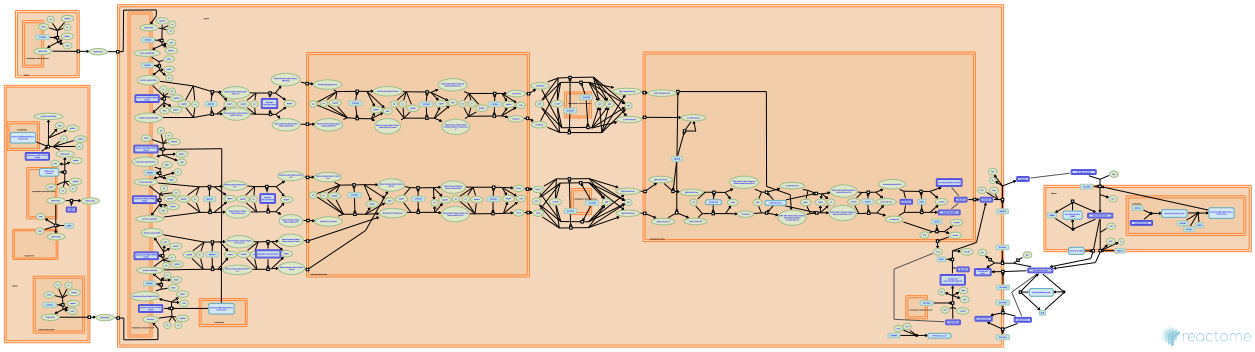
Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CYP51A1	Q16850	DHCR7	Q9UBM7	FDFT1	P37268
HMGCR	P04035-1	IDI1	Q13907	IDI2	Q13907
LBR	O76062	LSS	P48449	MVK	Q03426
PMVK	Q15126	SC5D	O75845	SQLE	Q14534
TM7SF2	O76062				

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
CYP51A1	ENSG00000001630	DHCR7	ENSG00000172893	FDFT1	ENSG00000079459
HMGCR	ENSG00000113161	IDI1	ENSG00000067064	LSS	ENSG00000160285
MVK	ENSG00000110921	PMVK	ENSG00000163344	SC5D	ENSG00000109929
SQLE	ENSG00000104549	TM7SF2	ENSG00000149809		

Bile acid and bile salt metabolism ↗

Location: Metabolism of steroids

Stable identifier: R-HSA-194068



In a healthy adult human, about 500 mg of cholesterol is converted to bile salts daily. Newly synthesized bile salts are secreted into the bile and released into the small intestine where they emulsify dietary fats (Russell 2003). About 95% of the bile salts in the intestine are recovered and returned to the liver (Kullak-Ublick et al. 2004; Trauner and Boyer 2002). The major pathway for bile salt synthesis in the liver begins with the conversion of cholesterol to 7alpha-hydroxycholesterol. Bile salt synthesis can also begin with the synthesis of an oxysterol - 24-hydroxycholesterol or 27-hydroxycholesterol. In the body, the initial steps of these two pathways occur in extrahepatic tissues, generating intermediates that are transported to the liver and converted to bile salts via the 7alpha-hydroxycholesterol pathway. These extrahepatic pathways contribute little to the total synthesis of bile salts, but are thought to play important roles in extrahepatic cholesterol homeostasis (Javitt 2002).

Literature references

Boyer, JL., Trauner, M. (2003). Bile salt transporters: molecular characterization, function, and regulation. *Physiol Rev, 83*, 633-671. ↗

Javitt, NB. (2002). Cholesterol, hydroxycholesterols, and bile acids. *Biochem Biophys Res Commun, 292*, 1147-53. ↗

Russell, DW. (2003). The enzymes, regulation, and genetics of bile acid synthesis. *Annu Rev Biochem, 72*, 137-74. ↗

Meier, PJ., Kullak-Ublick, GA., Stieger, B. (2004). Enterohepatic bile salt transporters in normal physiology and liver disease. *Gastroenterology, 126*, 322-42. ↗

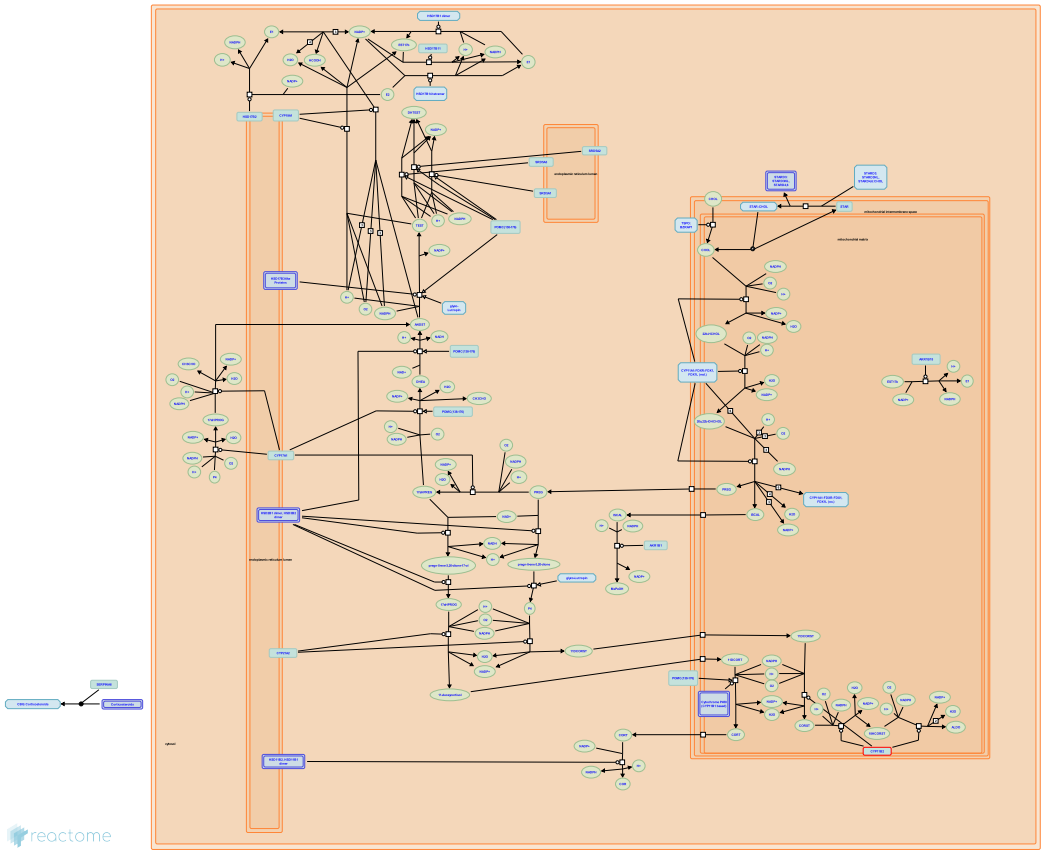
Editions

2007-01-19	Authored	Jassal, B.
2007-04-30	Edited, Reviewed	D'Eustachio, P.

Metabolism of steroid hormones ↗

Location: Metabolism of steroids

Stable identifier: R-HSA-196071



Steroid hormones are synthesized primarily in the adrenal gland and gonads. They regulate energy metabolism and stress responses (glucocorticoids), salt balance (mineralocorticoids), and sexual development and function (androgens and estrogens). All steroids are synthesized from cholesterol. Steroid hormone synthesis is largely regulated at the initial steps of cholesterol mobilization and transport into the mitochondrial matrix for conversion to pregnenolone. In the body, the fate of pregnenolone is tissue-specific: in the zona fasciculata of the adrenal cortex it is converted to cortisol, in the zona glomerulosa to aldosterone, and in the gonads to testosterone and then to estrone and estradiol. These pathways are outlined in the figure below, which also details the sites on the cholesterol molecule that undergo modification in the course of these reactions.

Literature references

Payne, AH., Hales, DB. (2004). Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. *Endocr Rev, 25*, 947-70. ↗

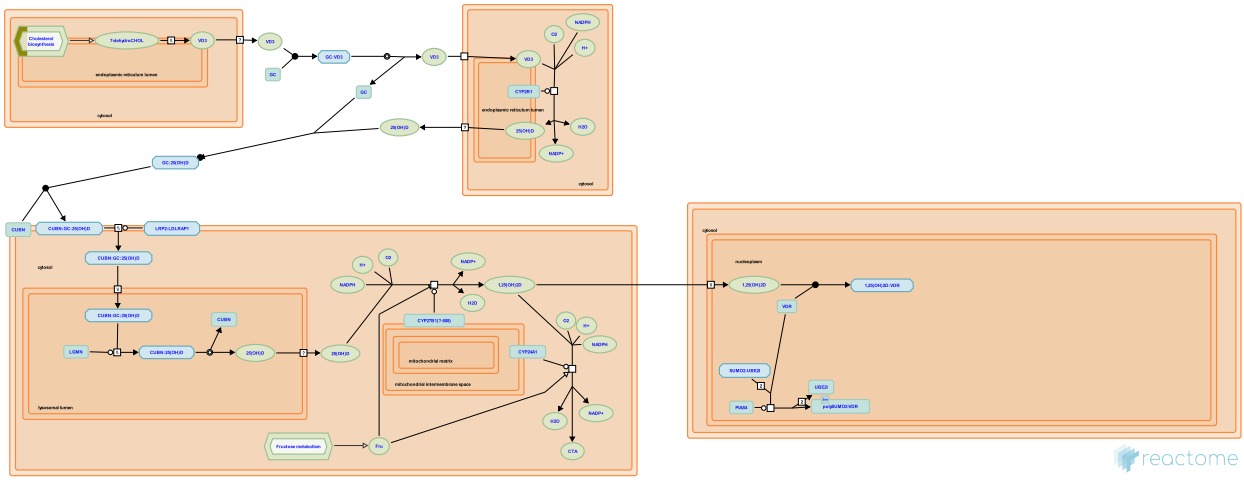
Editions

2007-04-20	Reviewed	D'Eustachio, P.
2007-04-20	Authored, Edited	Jassal, B.

Vitamin D (calciferol) metabolism ↗

Location: Metabolism of steroids

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.

Table of Contents

Introduction 1

Analysis properties 2

Metabolism of steroids 3

- Cholesterol biosynthesis 5
- Regulation of cholesterol biosynthesis by SREBP (SREBF) 7
- Bile acid and bile salt metabolism 9
- Metabolism of steroid hormones 10
- Vitamin D (calciferol) metabolism 11

Table of Contents 12