reactome

Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 80 on 15/05/2022. The web link to these results is:

https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMjA1MTQxNTM0MzNfNDkyOA%3D%3D

Please keep in mind that analysis results are temporarily stored on our server. The storage period depends on usage of the service but is at least 7 days. As a result, please note that this URL is only valid for a limited time period and it might have expired.

Table of Contents

1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for Homo sapiens are available for 17 non-human species including mouse, rat, chicken, puffer fish, worm, fly, yeast, rice, and Arabidopsis. Pathways are represented by simple diagrams following an SBGN-like format.

Reactome's annotated data describe reactions possible if all annotated proteins and small molecules were present and active simultaneously in a cell. By overlaying an experimental dataset on these annotations, a user can perform a pathway over-representation analysis. By overlaying quantitative expression data or time series, a user can visualize the extent of change in affected pathways and its progression. A binomial test is used to calculate the probability shown for each result, and the p-values are corrected for the multiple testing (Benjamini–Hochberg procedure) that arises from evaluating the submitted list of identifiers against every pathway.

To learn more about our Pathway Analysis, please have a look at our relevant publications:

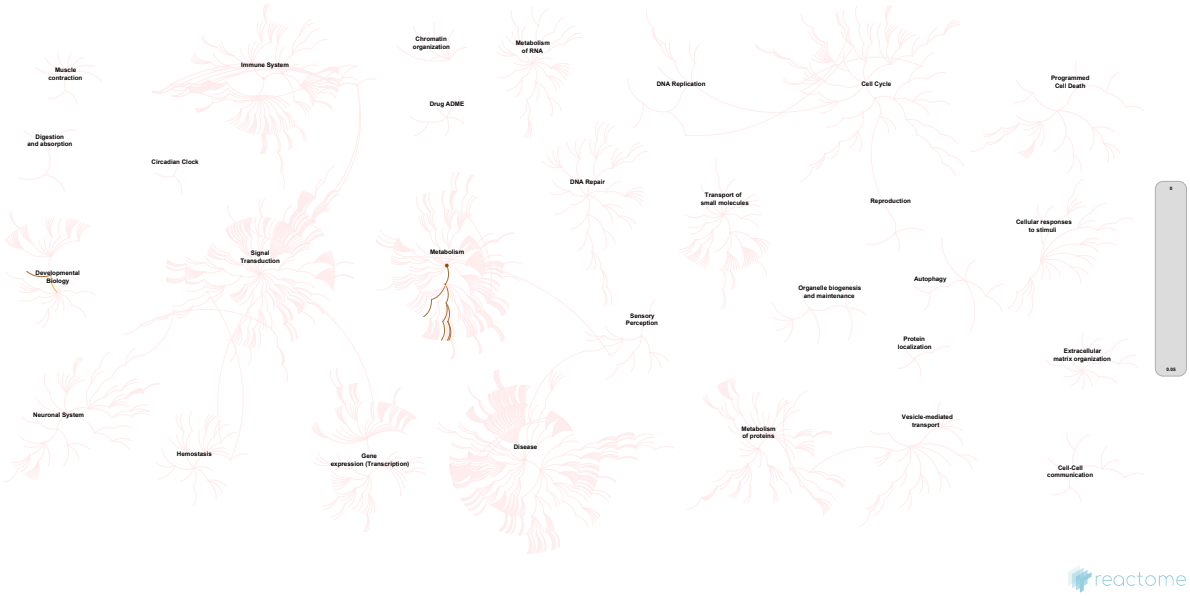
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, … D'Eustachio P (2016). The reactome pathway knowledgebase. Nucleic Acids Research, 44(D1), D481–D487. https://doi.org/10.1093/nar/gkv1351.

Fabregat A, Sidiropoulos K, Viteri G, Forner O, Marin-Garcia P, Arnau V, … Hermjakob H (2017). Reactome pathway analysis: a high-performance in-memory approach. BMC Bioinformatics, 18.

2. 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.
- 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.

3. Genome-wide overview



This figure shows a genome-wide overview of the results of your pathway analysis. Reactome pathways are arranged in a hierarchy. The center of each of the circular "bursts" is the root of one top-level pathway, for example "DNA Repair". Each step away from the center represents the next level lower in the pathway hierarchy. The color code denotes over-representation of that pathway in your input dataset. Light grey signifies pathways which are not significantly over-represented.

4. Most significant pathways

The following table shows the 25 most relevant pathways sorted by p-value.

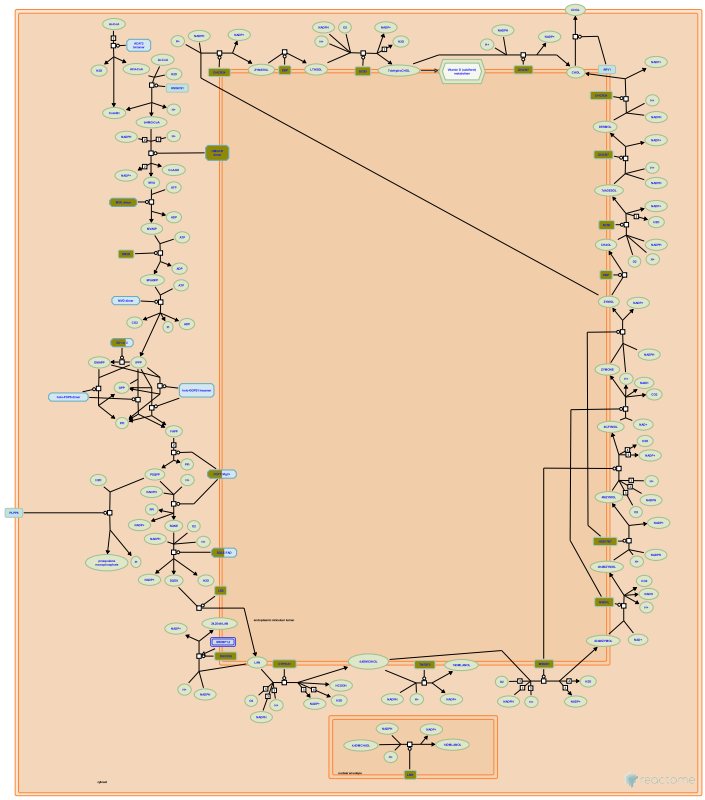
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Cholesterol biosynthesis	19 / 77	0.005	1.11e-16	8.88e-16	26 / 35	0.003
Activation of gene expression by SREBF (SREBP)	22 / 71	0.005	1.11e-16	8.88e-16	22 / 42	0.003
Regulation of cholesterol biosynthesis by SREBP (SREBF)	22 / 87	0.006	1.11e-16	8.88e-16	22 / 52	0.004
Metabolism of steroids	30 / 331	0.022	1.11e-16	8.88e-16	48 / 245	0.018
Metabolism of lipids	30 / 1,446	0.096	1.11e-16	8.88e-16	48 / 955	0.069
Metabolism	30 / 3,639	0.241	4.55e-15	2.73e-14	48 / 2,250	0.163
Cholesterol biosynthesis via desmosterol	4 / 14	9.27e-04	3.35e-08	1.67e-07	4 / 4	2.90e-04
Cholesterol biosynthesis via lathosterol	4 / 14	9.27e-04	3.35e-08	1.67e-07	4 / 4	2.90e-04
EGR2 and SOX10-mediated initiation of Schwann cell myelination	4 / 39	0.003	1.94e-06	7.75e-06	4 / 26	0.002
PPARA activates gene expression	4 / 175	0.012	6.33e-04	0.002	2 / 41	0.003
Regulation of lipid metabolism by PPARalpha	4 / 177	0.012	6.60e-04	0.002	2 / 44	0.003
Nervous system development	4 / 621	0.041	0.05	0.149	4 / 324	0.023
Initiation of Nuclear Envelope (NE) Reformation	1 / 27	0.002	0.059	0.168	2 / 7	5.07e-04
Regulation of MECP2 expression and activity	1 / 39	0.003	0.084	0.168	1 / 14	0.001
RHOD GTPase cycle	1 / 57	0.004	0.121	0.202	1 / 9	6.52e-04
Endogenous sterols	1 / 72	0.005	0.15	0.202	1 / 18	0.001
RHOG GTPase cycle	1 / 78	0.005	0.161	0.202	1 / 6	4.35e-04
RHOC GTPase cycle	1 / 79	0.005	0.163	0.202	1 / 6	4.35e-04
Nuclear Envelope (NE) Reassembly	1 / 88	0.006	0.18	0.202	2 / 24	0.002
RAC2 GTPase cycle	1 / 92	0.006	0.188	0.202	1 / 10	7.25e-04
RAC3 GTPase cycle	1 / 100	0.007	0.202	0.202	1 / 6	4.35e-04
Transcriptional Regulation by MECP2	1 / 100	0.007	0.202	0.202	1 / 77	0.006
RHOA GTPase cycle	1 / 154	0.01	0.294	0.294	1 / 6	4.35e-04
CDC42 GTPase cycle	1 / 159	0.011	0.302	0.302	1 / 6	4.35e-04
Developmental Biology	4 / 1,263	0.084	0.316	0.316	4 / 556	0.04

* False Discovery Rate

5. Pathways details

For every pathway of the most significant pathways, we present its diagram, as well as a short summary, its bibliography and the list of inputs found in it.

1. Cholesterol biosynthesis (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).

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.

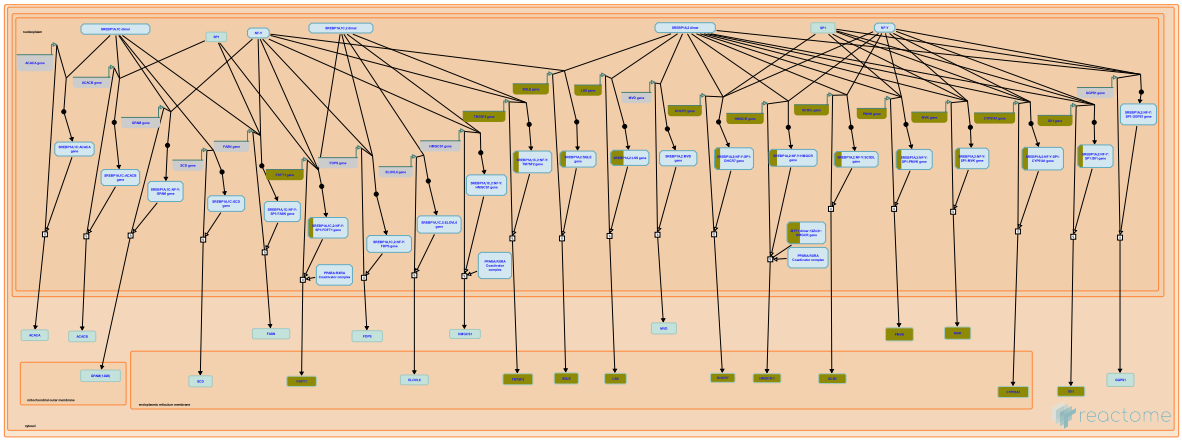
Edit history

Date	Action	Author
2007-01-19	Created	Jassal B
2007-01-22	Edited	D'Eustachio P
2007-01-22	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
2022-03-30	Modified	Weiser JD

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

2. Activation of gene expression by SREBF (SREBP) (R-HSA-2426168)



Cellular compartments: nucleoplasm.

After transiting to the nucleus SREBPs (SREBP1A/1C/2, SREBFs) bind short sequences, sterol regulatory elements (SREs), in the promoters of target genes (reviewed in Eberle et al. 2004, Weber et al. 2004). SREBPs alone are relatively weak activators of transcription, with SREBP1C being significantly weaker than SREBP1A or SREBP2. In combination with other transcription factors such as SP1 and NF-Y the SREBPs are much stronger activators. SREBP1C seems to more specifically target genes involved in fatty acid synthesis while SREBP2 seems to target genes involved in cholesterol synthesis (Pai et al. 1998).

References

Brown MS, Pai JT, Guryev O & Goldstein JL (1998). Differential stimulation of cholesterol and unsaturated fatty acid biosynthesis in cells expressing individual nuclear sterol regulatory element-binding proteins. J Biol Chem, 273, 26138-48.

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

Hegarty B, Ferré P, Foufelle F, Bossard P & Eberlé D (2004). SREBP transcription factors: master regulators of lipid homeostasis. Biochimie, 86, 839-48.

Edit history

Date	Action	Author
2012-07-26	Edited	May B
2012-07-26	Authored	May B
2012-07-27	Created	May B
2012-08-25	Reviewed	Liang G
2020-11-10	Modified	D'Eustachio P

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

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CYP51A1	Q16850	DHCR7	Q9UBM7	FDFT1	P37268
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PMVK	Q15126
TM7SF2	O76062

Input	UniProt Id
SC5D	O75845

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SQLE	Q14534

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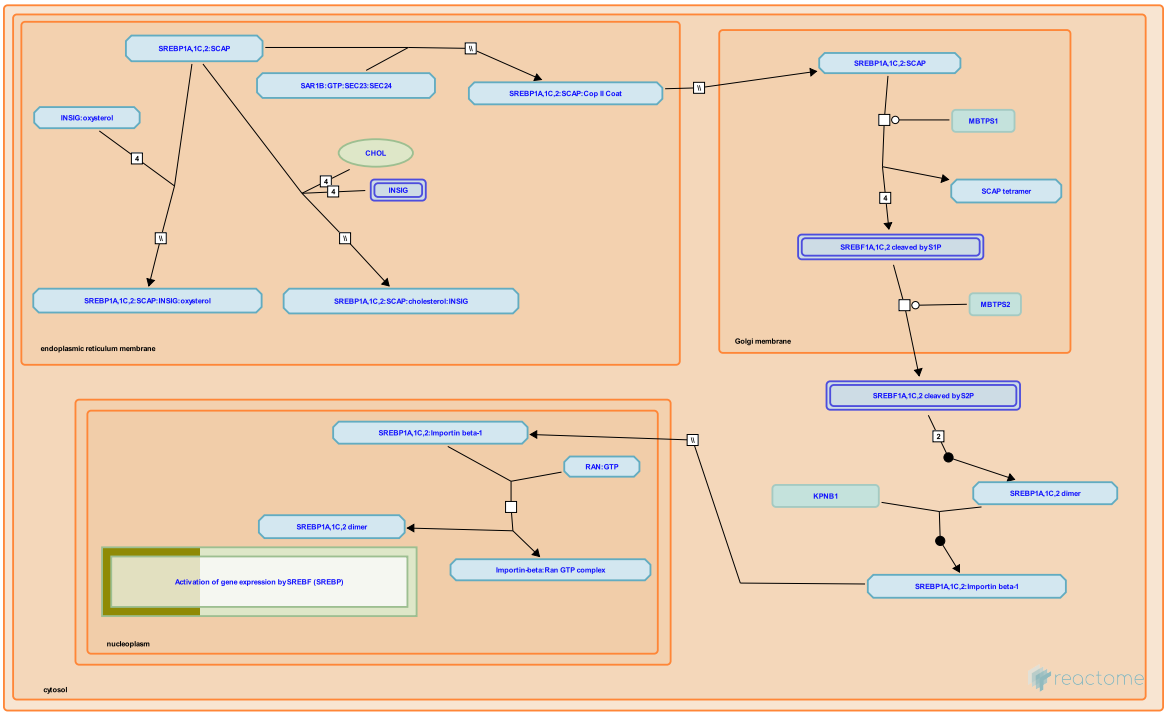
MVK	ENSG00000110921
SQLE	ENSG00000104549

Input	Ensembl Id
DHCR7	ENSG00000172893
IDI1	ENSG00000067064
PMVK	ENSG00000163344
TM7SF2	ENSG00000149809

Input	Ensembl Id
FDFT1	ENSG00000079459
LSS	ENSG00000160285
SC5D	ENSG00000109929

3. Regulation of cholesterol biosynthesis by SREBP (SREBF) (R-HSA-1655829)



Cellular 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.

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.

Edit history

Date	Action	Author
2011-09-28	Authored	May B
2011-10-13	Edited	May B
2011-10-13	Created	May B
2012-08-25	Reviewed	Liang G
2022-03-23	Modified	Weiser JD

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

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HMGCR	P04035-1
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PMVK	Q15126
TM7SF2	O76062

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SC5D	O75845

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IDI2	Q13907
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SQLE	Q14534

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HMGCR	ENSG00000113161
MVK	ENSG00000110921
SQLE	ENSG00000104549

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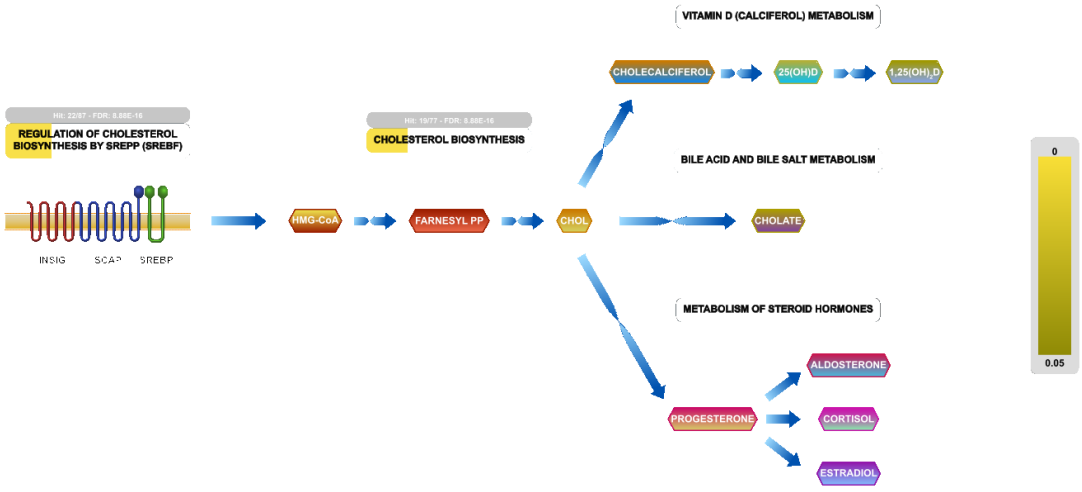
DHCR7	ENSG00000172893
IDI1	ENSG00000067064
PMVK	ENSG00000163344
TM7SF2	ENSG00000149809

Input	Ensembl Id
FDFT1	ENSG00000079459
LSS	ENSG00000160285
SC5D	ENSG00000109929

4. Metabolism of steroids (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 (hydroxymethyl-glutaryl-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).

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.

Edit history

Date	Action	Author
2007-01-24	Edited	Jassal B
2007-01-24	Authored	Jassal B
2015-11-02	Reviewed	Jassal B
2017-01-24	Created	D'Eustachio P
2022-03-23	Modified	Weiser JD

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

Input	UniProt Id
CYP51A1	Q16850
EBP	Q15125
HSD17B7	P56937
LBR	O76062, Q14739
MVK	Q03426
SC5D	O75845

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DHCR24	Q15392
FDFT1	P37268
IDI1	Q13907
LSS	P48449
NSDHL	Q15738
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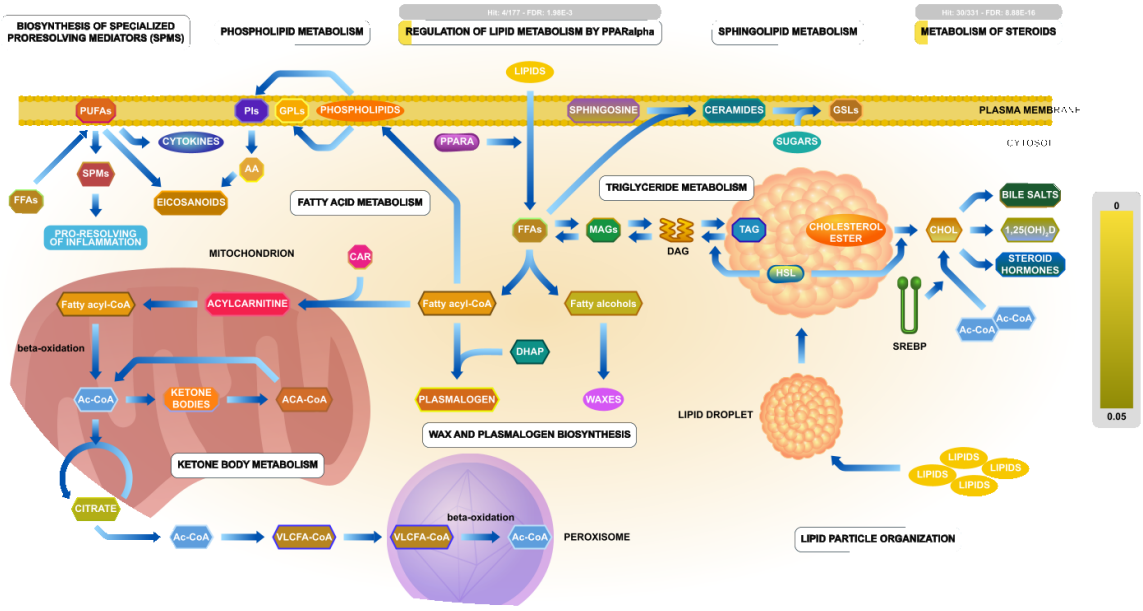
IDI1	ENSG00000067064
PMVK	ENSG00000163344
TM7SF2	ENSG00000149809

Input	Ensembl Id
FDFT1	ENSG00000079459
LSS	ENSG00000160285
SC5D	ENSG00000109929

5. Metabolism of lipids (R-HSA-556833)



Lipids are hydrophobic but otherwise chemically diverse molecules that play a wide variety of roles in human biology. They include ketone bodies, fatty acids, triacylglycerols, phospholipids and sphingolipids, eicosanoids, cholesterol, bile salts, steroid hormones, and fat-soluble vitamins. They function as a major source of energy (fatty acids, triacylglycerols, and ketone bodies), are major constituents of cell membranes (cholesterol and phospholipids), play a major role in their own digestion and uptake (bile salts), and participate in numerous signaling and regulatory processes (steroid hormones, eicosanoids, phosphatidylinositols, and sphingolipids) (Vance & Vance 2008 - URL).

The central steroid in human biology is cholesterol, obtained from animal fats consumed in the diet or synthesized de novo from acetyl-coenzyme A. (Vegetable fats contain various sterols but no cholesterol.) Cholesterol is an essential constituent of lipid bilayer membranes and is the starting point for the biosyntheses of bile acids and salts, steroid hormones, and vitamin D. Bile acids and salts are mostly synthesized in the liver. They are released into the intestine and function as detergents to solubilize dietary fats. Steroid hormones are mostly synthesized 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). At the same time, chronically elevated cholesterol levels in the body are associated with the formation of atherosclerotic lesions and hence increased risk of heart attacks and strokes. The human body lacks a mechanism for degrading excess cholesterol, although an appreciable amount is lost daily in the form of bile salts and acids that escape recycling.

Aspects of lipid metabolism currently annotated in Reactome include lipid digestion, mobilization, and transport; fatty acid, triacylglycerol, and ketone body metabolism; peroxisomal lipid metabolism; phospholipid and sphingolipid metabolism; cholesterol biosynthesis; bile acid and bile salt metabolism; and steroid hormone biosynthesis.

References

Biochemistry of Lipids, Lipoproteins and Membranes (Fifth Edition). Retrieved from http://www.sciencedirect.com/science/book/9780444532190

Edit history

Date	Action	Author
2007-02-02	Authored	Jassal B, Gopinathrao G, D'Eustachio P, Gillespie ME
2010-03-23	Created	D'Eustachio P
2017-02-20	Revised	D'Eustachio P
2022-03-10	Edited	Joshi-Tope G, D'Eustachio P
2022-03-23	Modified	Weiser JD

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

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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
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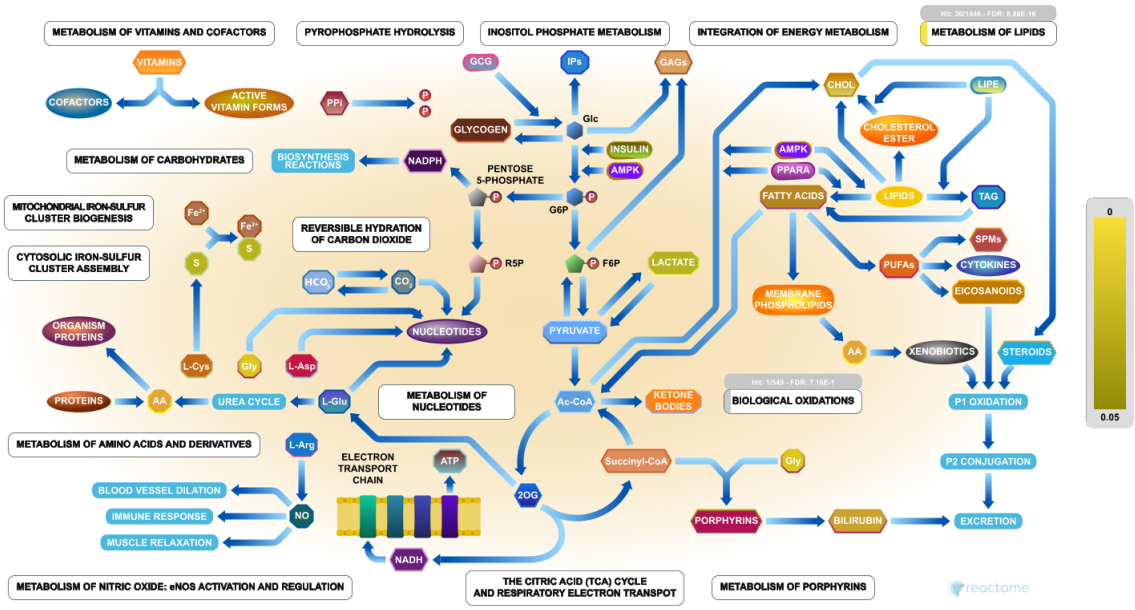
MVK	ENSG00000110921	PMVK	ENSG00000163344	SC5D	ENSG00000109929
SQLE	ENSG00000104549	TM7SF2	ENSG00000149809		

6. Metabolism (R-HSA-1430728)



Metabolic processes in human cells generate energy through the oxidation of molecules consumed in the diet and mediate the synthesis of diverse essential molecules not taken in the diet as well as the inactivation and elimination of toxic ones generated endogenously or present in the extracellular environment. The processes of energy metabolism can be classified into two groups according to whether they involve carbohydrate-derived or lipid-derived molecules, and within each group it is useful to distinguish processes that mediate the breakdown and oxidation of these molecules to yield energy from ones that mediate their synthesis and storage as internal energy reserves. Synthetic reactions are conveniently grouped by the chemical nature of the end products, such as nucleotides, amino acids and related molecules, and porphyrins. Detoxification reactions (biological oxidations) are likewise conveniently classified by the chemical nature of the toxin.

At the same time, all of these processes are tightly integrated. Intermediates in reactions of energy generation are starting materials for biosyntheses of amino acids and other compounds, broad-specificity oxidoreductase enzymes can be involved in both detoxification reactions and biosyntheses, and hormone-mediated signaling processes function to coordinate the operation of energy-generating and energy-storing reactions and to couple these to other biosynthetic processes.

References

Edit history

Date	Action	Author
2011-07-07	Created	Jassal B
2022-03-23	Modified	Weiser JD

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

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HSD17B7	P56937	IDI1	Q13907	IDI2	Q13907, Q9BXS1

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NSDHL	Q15738
SQLE	Q14534

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PMVK	Q15126
TM7SF2	O76062

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MVK	ENSG00000110921
SQLE	ENSG00000104549

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IDI1	ENSG00000067064
PMVK	ENSG00000163344
TM7SF2	ENSG00000149809

Input	Ensembl Id
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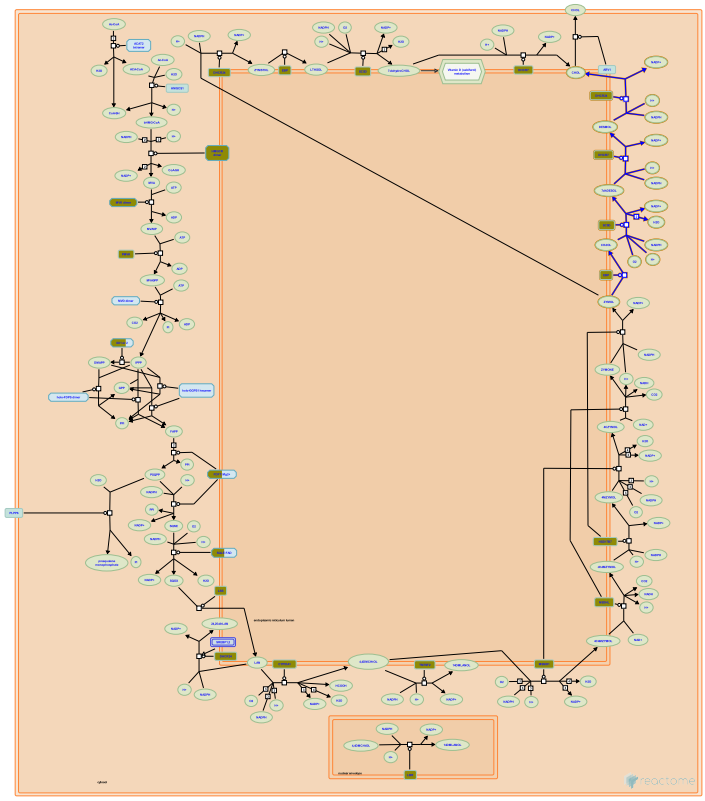
LSS	ENSG00000160285
SC5D	ENSG00000109929

7. Cholesterol biosynthesis via desmosterol (R-HSA-6807047)



Cellular compartments: endoplasmic reticulum membrane, cytosol.

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 (Mitsche et al. 2015).

References

Hobbs HH, Mitsche MA, Cohen JC & McDonald JG (2015). Flux analysis of cholesterol biosynthesis in vivo reveals multiple tissue and cell-type specific pathways. Elife, 4, e07999.

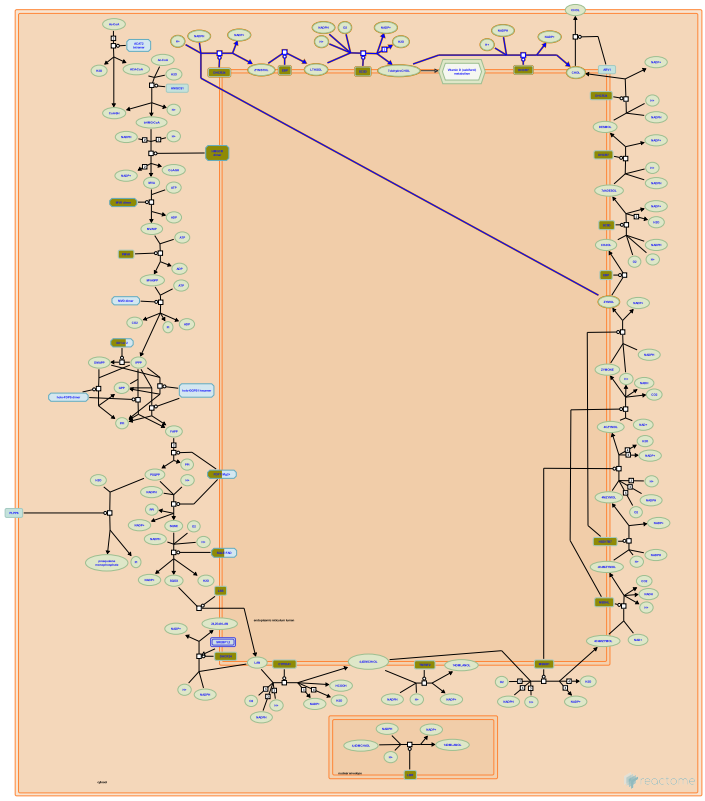
Edit history

Date	Action	Author
2015-10-28	Created	D'Eustachio P
2015-11-02	Edited	D'Eustachio P
2015-11-02	Reviewed	Jassal B
2015-11-02	Authored	D'Eustachio P
2022-03-23	Modified	Weiser JD

4 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id	Input	UniProt Id
DHCR24	Q15392	DHCR7	Q9UBM7
EBP	Q15125	SC5D	O75845

8. Cholesterol biosynthesis via lathosterol (R-HSA-6807062)



Cellular compartments: endoplasmic reticulum membrane, cytosol.

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 (Kandutsch & Russell 1960; Mitsche et al. 2015).

References

Russell AE & Kandutsch AA (1960). Preputial gland tumor sterols. 3. A metabolic pathway from lanosterol to cholesterol. J. Biol. Chem., 235, 2256-61.

Hobbs HH, Mitsche MA, Cohen JC & McDonald JG (2015). Flux analysis of cholesterol biosynthesis in vivo reveals multiple tissue and cell-type specific pathways. Elife, 4, e07999.

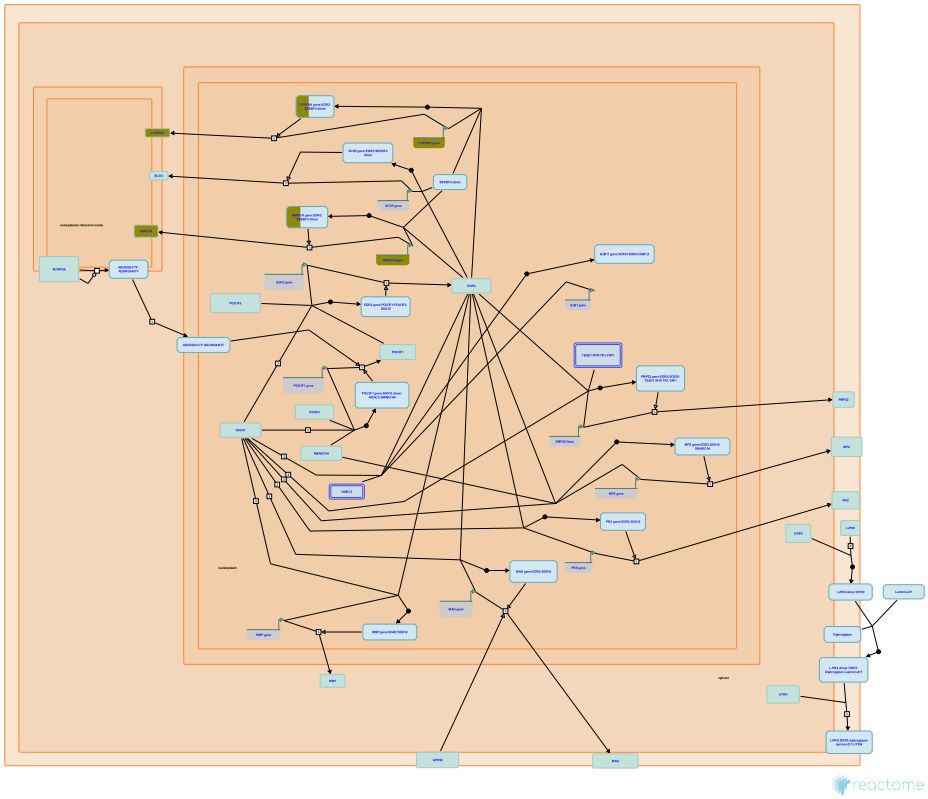
Edit history

Date	Action	Author
2015-10-28	Created	D'Eustachio P
2015-11-02	Edited	D'Eustachio P
2015-11-02	Reviewed	Jassal B
2015-11-02	Authored	D'Eustachio P
2022-03-23	Modified	Weiser JD

4 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id	Input	UniProt Id
DHCR24	Q15392	DHCR7	Q9UBM7
EBP	Q15125	SC5D	O75845

9. EGR2 and SOX10-mediated initiation of Schwann cell myelination (R-HSA-9619665)



Schwann cells are glial cells of the peripheral nervous system that ensheath the peripheral nerves within a compacted lipid-rich myelin structure that is required for optimal transduction of nerve signals in motor and sensory nerves. Schwann cells develop from the neural crest in a differentiation process driven by factors derived from the Schwann cell itself, from the adjacent neuron or from the extracellular matrix (reviewed in Jessen and Mirsky, 2005). Upon peripheral nerve injury, mature Schwann cells can form repair cells that allow peripheral nerve regeneration through myelin phagocytosis and remyelination of the peripheral nerve. This process in some ways recapitulates the maturation of immature Schwann cells during development (reviewed in Jessen and Mirsky, 2016). Mature, fully myelinated Schwann cells exhibit longitudinal and radial polarization. The axon-distal abaxonal membrane interacts with elements of the basal lamina through integrins and lamins and in this way resembles the basolateral domain of polarized epithelial cells. In contrast, the axon-proximal adaxonal membrane resembles the apical domain of an epithelial cell, and is enriched with adhesion molecules and receptors that mediate interaction with ligands from the axon (reviewed in Salzer, 2015).

Schwann cells express a number of Schwann-cell specific proteins, including components of the myelin sheath such as myelin basic protein (MBP) and myelin protein zero (MPZ). In addition, Schwann cells have high lipid content relative to other membranes, and are enriched in galactosphingolipids, cholesterol and saturated long chain fatty acids (reviewed in Garbay et al, 2000). This protein and lipid profile is driven by a Schwann cell myelination transcriptional program controlled by master regulators SOX10, POU3F1 and EGR2, among others (reviewed in Svaren and Meijer, 2008; Stolt and Wegner, 2016).

References

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Cassagne C, Sargueil F, Heape AM & Garbay B (2000). Myelin synthesis in the peripheral nervous system. Prog. Neurobiol., 61, 267-304.

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Wegner M & Stolt CC (2016). Schwann cells and their transcriptional network: Evolution of key regulators of peripheral myelination. Brain Res., 1641, 101-110.

Edit history

Date	Action	Author
2018-09-18	Created	Rothfels K
2019-08-16	Authored	Rothfels K
2020-01-17	Reviewed	Aletta J M
2020-02-24	Edited	Rothfels K
2022-03-23	Modified	Weiser JD

2 submitted entities found in this pathway, mapping to 4 Reactome entities

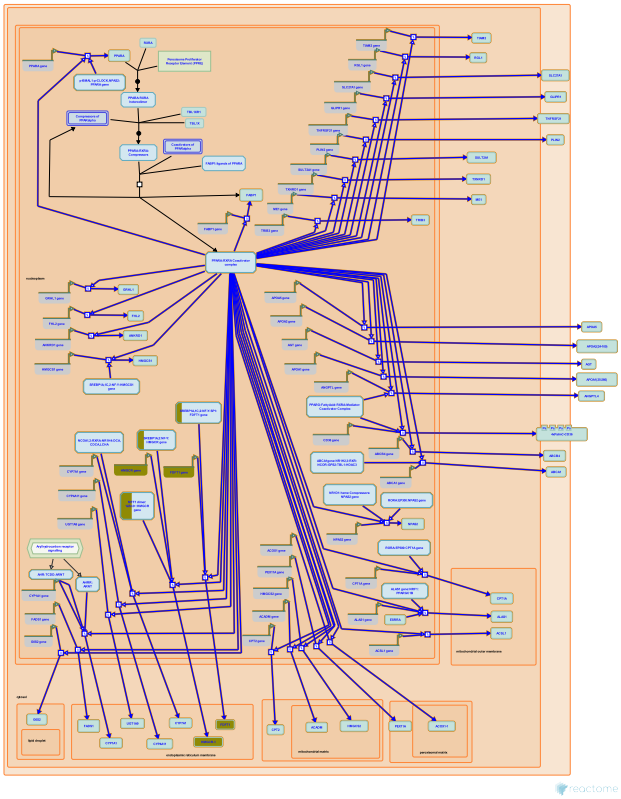
Input	UniProt Id
CYP51A1	Q16850

Input	UniProt Id
HMGCR	P04035

Input	Ensembl Id
CYP51A1	ENSG00000001630

Input	Ensembl Id
HMGCR	ENSG00000113161

10. PPARA activates gene expression (R-HSA-1989781)



Cellular compartments: peroxisomal matrix, endoplasmic reticulum membrane, plasma membrane, nucleoplasm, mitochondrial outer membrane, cytosol, mitochondrial matrix, extracellular region, lipid droplet, mitochondrial inner membrane, peroxisomal membrane.

The set of genes regulated by PPAR-alpha is not fully known in humans, however many examples have been found in mice. Genes directly activated by PPAR-alpha contain peroxisome proliferator receptor elements (PPREs) in their promoters and include:

1) genes involved in fatty acid oxidation and ketogenesis (Acox1, Cyp4a, Acadm, Hmgcs2);

2) genes involved in fatty acid transport (Cd36, , Slc27a1, Fabp1, Cpt1a, Cpt2);

3) genes involved in producing fatty acids and very low density lipoproteins (Me1, Scd1);

4) genes encoding apolipoproteins (Apoa1, Apoa2, Apoa5);

5) genes involved in triglyceride clearance (Angptl4);

6) genes involved in glycerol metabolism (Gpd1 in mouse);

7) genes involved in glucose metabolism (Pdk4);

8) genes involved in peroxisome proliferation (Pex11a);

9) genes involved in lipid storage (Plin, Adfp).

Many other genes are known to be regulated by PPAR-alpha but whether their regulation is direct or indirect remains to be found. These genes include: ACACA, FAS, SREBP1, FADS1, DGAT1, ABCA1, PLTP, ABCB4, UGT2B4, SULT2A1, Pnpla2, Acsl1, Slc27a4, many Acot genes, and others (reviewed in Rakhshandehroo et al. 2010).

References

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Wahli W & Desvergne B (1999). Peroxisome proliferator-activated receptors: nuclear control of metabolism. Endocr Rev, 20, 649-88.

Kersten S, Knoch B, Rakhshandehroo M & Müller M (2010). Peroxisome proliferator-activated receptor alpha target genes. PPAR Res, 2010.

Qi C, Reddy JK & Zhu Y (2000). Peroxisome proliferator-activated receptors, coactivators, and downstream targets. Cell Biochem Biophys, 32, 187-204.

Kersten S (2008). Peroxisome proliferator activated receptors and lipoprotein metabolism. PPAR Res, 2008, 132960.

Edit history

Date	Action	Author
2009-06-08	Reviewed	Kersten S
2011-11-08	Edited	May B
2011-11-08	Authored	May B
2011-11-13	Created	May B
2020-11-10	Modified	D'Eustachio P

2 submitted entities found in this pathway, mapping to 4 Reactome entities

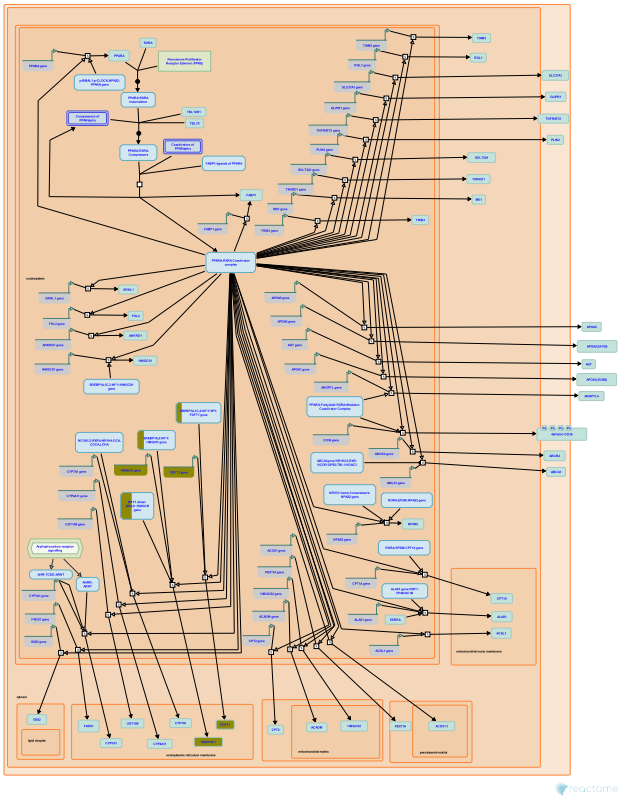
Input	UniProt Id
FDFT1	P37268

Input	UniProt Id
HMGCR	P04035-1

Input	Ensembl Id
FDFT1	ENSG00000079459

Input	Ensembl Id
HMGCR	ENSG00000113161

11. Regulation of lipid metabolism by PPARalpha (R-HSA-400206)



Cellular compartments: nucleoplasm, cytosol.

Peroxisome proliferator-activated receptor alpha (PPAR-alpha) is the major regulator of fatty acid oxidation in the liver. PPARalpha is also the target of fibrate drugs used to treat abnormal plasma lipid levels.

PPAR-alpha is a type II nuclear receptor (its subcellular location does not depend on ligand binding). PPAR-alpha forms heterodimers with Retinoid X receptor alpha (RXR-alpha), another type II nuclear receptor. PPAR-alpha is activated by binding fatty acid ligands, especially polyunsaturated fatty acids having 18-22 carbon groups and 2-6 double bonds.

The PPAR-alpha:RXR-alpha heterodimer binds peroxisome proliferator receptor elements (PPREs) in and around target genes. Binding of fatty acids and synthetic ligands causes a conformational change in PPAR-alpha such that it releases the corepressors and binds coactivators (CBP-SRC-HAT complex, ASC complex, and TRAP-Mediator complex) which initiate transcription of the target genes.

Target genes of PPAR-alpha participate in fatty acid transport, fatty acid oxidation, triglyceride clearance, lipoprotein production, and cholesterol homeostasis.

References

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Gelman L, Wahli W, Michalik L, Desvergne B & Feige JN (2006). From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions. Prog Lipid Res, 45, 120-59.

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Kersten S (2008). Peroxisome proliferator activated receptors and lipoprotein metabolism. PPAR Res, 2008, 132960.

Edit history

Date	Action	Author
2009-03-24	Created	May B
2009-05-30	Edited	May B
2009-05-30	Authored	May B
2009-06-08	Edited	May B
2009-06-08	Reviewed	Kersten S
2011-11-08	Edited	May B
2011-11-13	Revised	May B
2022-03-23	Modified	Weiser JD

2 submitted entities found in this pathway, mapping to 4 Reactome entities

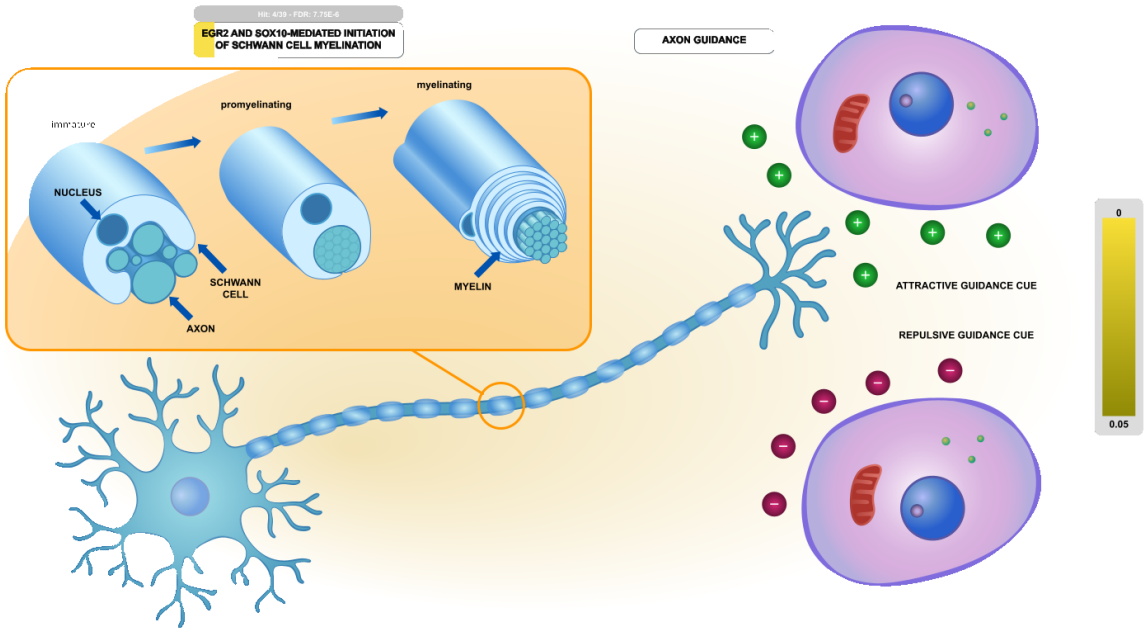
Input	UniProt Id
FDFT1	P37268

Input	UniProt Id
HMGCR	P04035-1

Input	Ensembl Id
FDFT1	ENSG00000079459

Input	Ensembl Id
HMGCR	ENSG00000113161

12. Nervous system development (R-HSA-9675108)



Neurogenesis is the process by which neural stem cells give rise to neurons, and occurs both during embryonic and perinatal development as well as in specific brain lineages during adult life (reviewed in Gotz and Huttner, 2005; Yao et al, 2016; Kriegstein and Alvarez-Buylla, 2009).

References

Götz M & Huttner WB (2005). The cell biology of neurogenesis. Nat. Rev. Mol. Cell Biol., 6, 777-88.

Kriegstein A & Alvarez-Buylla A (2009). The glial nature of embryonic and adult neural stem cells. Annu. Rev. Neurosci., 32, 149-84.

Christian KM, Ming GL, Yao B, Song H, Jin P & He C (2016). Epigenetic mechanisms in neurogenesis. Nat. Rev. Neurosci., 17, 537-49.

Edit history

Date	Action	Author
2020-01-23	Reviewed	Orlic-Milacic M
2020-01-31	Edited	Rothfels K
2020-01-31	Authored	Rothfels K
2020-01-31	Created	Rothfels K
2022-03-23	Modified	Weiser JD

2 submitted entities found in this pathway, mapping to 4 Reactome entities

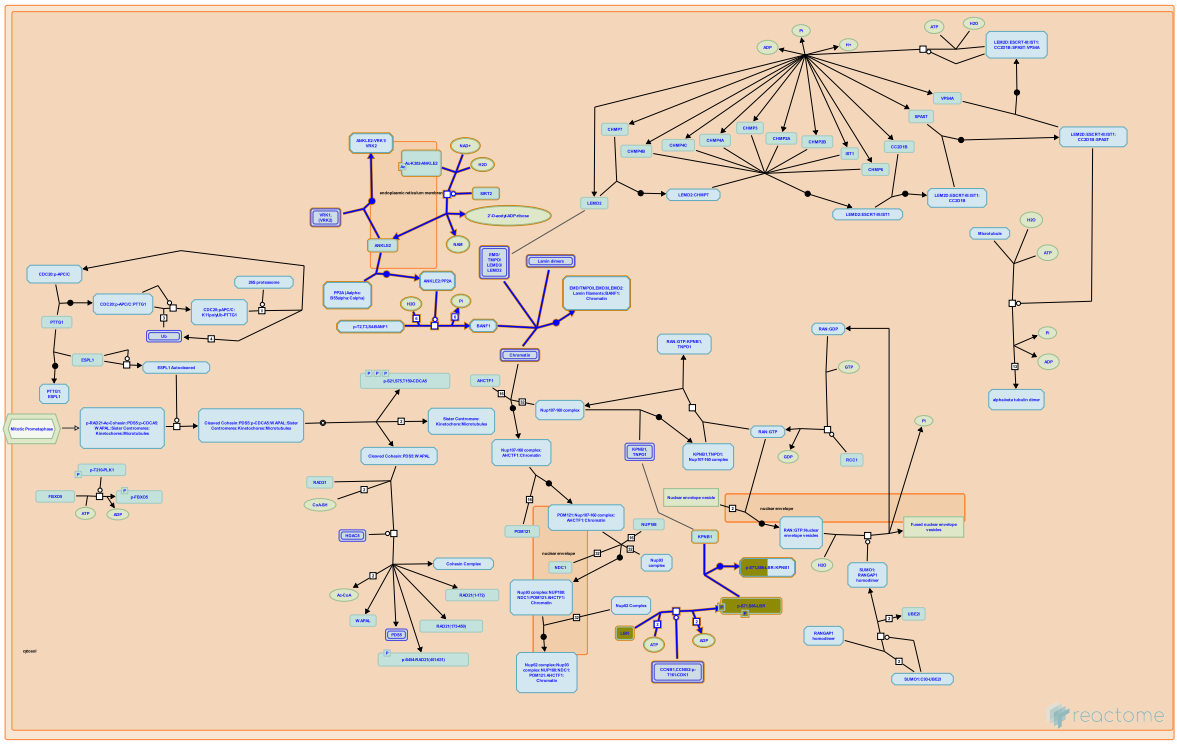
Input	UniProt Id
CYP51A1	Q16850

Input	UniProt Id
HMGCR	P04035

Input	Ensembl Id
CYP51A1	ENSG00000001630

Input	Ensembl Id
HMGCR	ENSG00000113161

13. Initiation of Nuclear Envelope (NE) Reformation (R-HSA-2995383)



Reassembly of the nuclear envelope (NE) is initiated at late anaphase/early telophase when BANF1 (BAF), which is dispersed throughout the cytoplasm during metaphase, accumulates on the surfaces of coalesced chromosomes. This is coordinated with the chromatin association of membranes and inner nuclear membrane proteins that include EMD (emerin), TMPO (LAP2beta), LEMD3 (MAN1) and LEMD2 (LEM2), and lamins (Haraguchi et al. 2008, reviewed by Wandke and Kutay 2013). The DNA-cross-bridging activity of BANF1 is required for individual chromosomes to properly coalesce for enclosure in a single nucleus (Samwer et al. 2017).

References

Wandke C & Kutay U (2013). Enclosing chromatin: reassembly of the nucleus after open mitosis. Cell, 152, 1222-5.

Hiraoka Y, Haraguchi T, Osakada H, Koujin T, Mori C, Kojidani T, ... Yamamoto A (2008). Live cell imaging and electron microscopy reveal dynamic processes of BAF-directed nuclear envelope assembly. J. Cell. Sci., 121, 2540-54.

Zuber J, Jude JG, Hoefler R, Samwer M, Gerlich DW, Schmalhorst PS & Schneider MWG (2017). DNA Cross-Bridging Shapes a Single Nucleus from a Set of Mitotic Chromosomes. Cell, 170, 956-972.e23.

Edit history

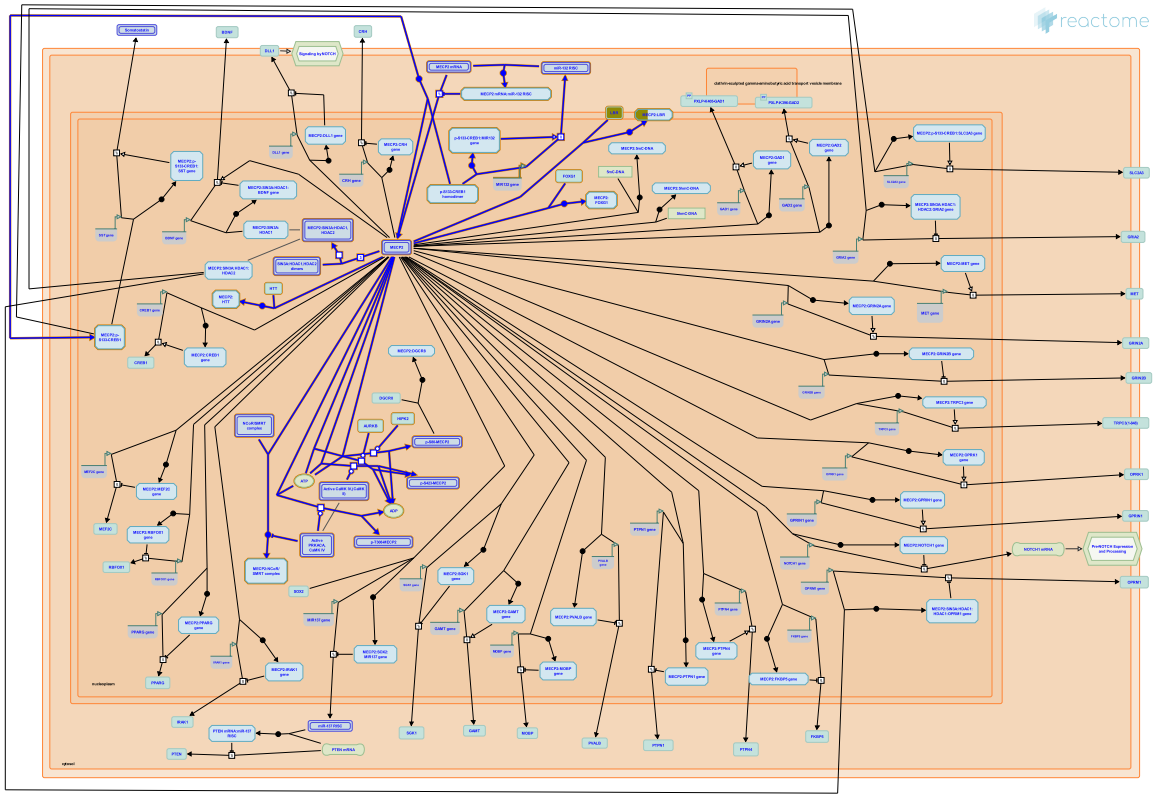
Date	Action	Author
2013-01-22	Authored	Orlic-Milacic M
2013-01-22	Created	Orlic-Milacic M
2013-01-23	Edited	Gillespie ME
2013-01-30	Reviewed	Gorjánácz M, Mattaj IW

Date	Action	Author
2019-11-06	Revised	Gerace L
2019-11-26	Edited	Orlic-Milacic M
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

14. Regulation of MECP2 expression and activity (R-HSA-9022692)



Transcription of the MECP2 gene is known to be regulated by methylation of the promoter and the first intron, but the responsible methyltransferases are not known (Nagarajan et al. 2008, Franklin et al. 2010, Liyanage et al. 2013).

Translation of MECP2 mRNA is negatively regulated by the microRNA miR-132. Transcription of miR-132 is regulated by BDNF signaling, through an unknown mechanism (Klein et al. 2007, Su et al. 2015).

Binding of MECP2 to other proteins and to DNA is regulated by posttranslational modifications, of which phosphorylation has been best studied. Calcium dependent protein kinases, PKA and CaMK IV, activated by neuronal membrane depolarization, phosphorylate MECP2 at threonine residue T308 (corresponding to T320 in the longer MECP2 splicing isoform, MECP2_e1). Phosphorylation at T308 correlates with neuronal activity and inhibits binding of MECP2 to the nuclear receptor co-repressor complex (NCoR/SMRT) (Ebert et al. 2013). In resting neurons, MECP2 is phosphorylated at serine residue S80, which results in a decreased association of MECP2 with chromatin. Nuclear serine/threonine protein kinase HIPK2 phosphorylates MECP2 on serine residue S80 (Bracaglia et al. 2009). In activity-induced neurons, upon neuronal membrane depolarization, MECP2 S80 becomes dephosphorylated, and MECP2 acquires phosphorylation on serine S423 (corresponding to mouse Mecp2 serine S421). CaMK IV is one of the kinases that can phosphorylate MECP2 on S423. Phosphorylation of MECP2 at S423 increases MECP2 binding to chromatin (Zhou et al. 2006, Tao et al. 2009, Qiu et al. 2012). AURKB phosphorylates MECP2 at serine residue S423 in dividing adult neuronal progenitor cells (Li et al. 2014).

Besides binding to the NCoR/SMRT co-repressor complex (Lyst et al. 2013, Ebert et al. 2013), MECP2 binds the SIN3A co-repressor complex. This interaction involves the transcriptional repressor domain of MECP2 and the amino terminal part of the HDAC interaction domain (HID) of SIN3A. HDAC1 and HDAC2 are part of the SIN3A co-repressor complex that co-immunoprecipitates with MECP2 (Nan et al. 1998). While binding of MECP2 to SIN3A at target genes is associated with transcriptional repression, binding to CREB1 at target genes is associated with transcriptional activation (Chahrour et al. 2008, Chen et al. 2013). Function of MECP2 can be affected by binding to FOXG1, another gene mutated in Rett syndrome besides MECP2 and CDKL5 (Dastidar et al. 2012), and HTT (Huntingtin) (McFarland et al. 2013). The subnuclear localization of MECP2 may be affected by binding to the Lamin B receptor (LBR) (Guarda et al. 2009).

References

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Huizenga MN, Sangrey GR, Darnell SB, Cha JH, Sadri-Vakili G, McFarland KN, ... Berezovska O (2014). MeCP2: a novel Huntingtin interactor. Hum. Mol. Genet., 23, 1036-44.

Impey S, Mandel G, Lioy DT, Klein ME, Goodman RH & Ma L (2007). Homeostatic regulation of MeCP2 expression by a CREB-induced microRNA. Nat. Neurosci., 10, 1513-4.

Patzel KA, Hansen RL, Jiang R, Van de Water J, Swanberg SE, Robinson WP, ... Yasui DH (2008). MECP2 promoter methylation and X chromosome inactivation in autism. Autism Res, 1, 169-78.

Ghosh A, Qiu Z, Zhang Y, Liu XY, Lieberman DN & Sylwestrak EL (2012). The Rett syndrome protein MeCP2 regulates synaptic scaling. J. Neurosci., 32, 989-94.

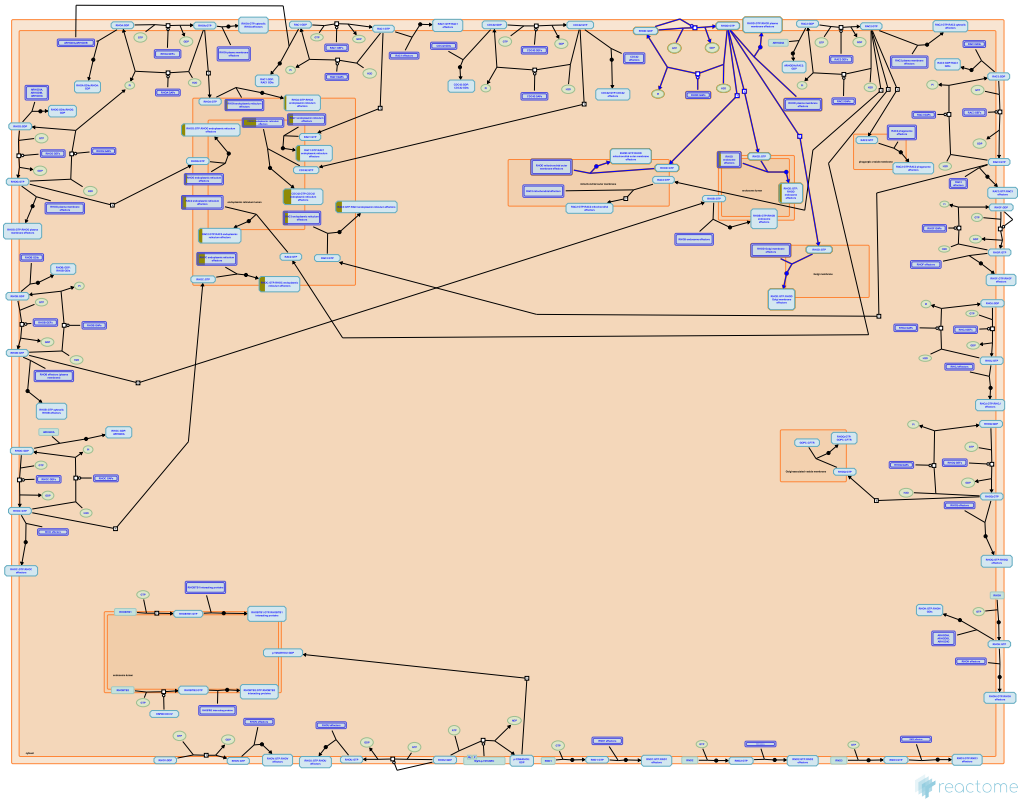
Edit history

Date	Action	Author
2017-09-25	Created	Orlic-Milacic M
2017-10-02	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2022-03-22	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

15. RHOD GTPase cycle (R-HSA-9013405)



This pathway catalogues RHOD GTPase activator proteins (GAPs) and RHOD effectors. RHOD possesses GTPase activity and is therefore grouped with classical RHO GTPases but it is atypical in the sense that no known guanine nucleotide exchange factors (GEFs) and no GDP dissociation inhibitors (GDIs) (Blom et al. 2017) are involved in the regulation of RHOD activity. RHOD possesses an elevated intrinsic guanine nucleotide exchange activity and auto-activates (Jaiswal, Fansa et al. 2013). RHOD regulates cytoskeletal dynamics and intracellular transport of vesicles (Gad and Aspenstrom 2010; Aspenstrom et al. 2014), especially actin-dependent movement of endosomes (Gasman et al. 2003, reviewed in Randazzo 2003).

References

Aspenström P (2014). Atypical Rho GTPases RhoD and Rif integrate cytoskeletal dynamics and membrane trafficking. Biol. Chem., 395, 477-84.

Randazzo PA (2003). RhoD, Src, and hDia2C in endosome motility. Dev. Cell, 4, 287-8.

Gad AK & Aspenström P (2010). Rif proteins take to the RhoD: Rho GTPases at the crossroads of actin dynamics and membrane trafficking. Cell. Signal., 22, 183-9.

Blom M, Reis K, Kreuger J, Heldin J & Aspenström P (2017). The atypical Rho GTPase RhoD is a regulator of actin cytoskeleton dynamics and directed cell migration. Exp. Cell Res., 352, 255-264.

Ahmadian MR, Jaiswal M, Fansa EK & Dvorsky R (2013). New insight into the molecular switch mechanism of human Rho family proteins: shifting a paradigm. Biol. Chem., 394, 89-95.

Edit history

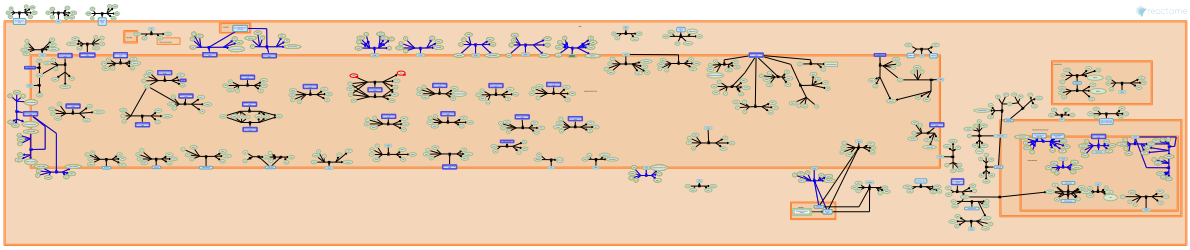
Date	Action	Author
2017-07-24	Created	Orlic-Milacic M

Date	Action	Author
2020-07-14	Authored	Orlic-Milacic M
2021-02-04	Reviewed	Fort P
2021-02-19	Reviewed	Bisbal M
2021-02-25	Edited	Orlic-Milacic M
2021-03-26	Revised	Orlic-Milacic M
2021-03-26	Edited	Orlic-Milacic M
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

16. Endogenous sterols (R-HSA-211976)



Cellular compartments: endoplasmic reticulum membrane, mitochondrial inner membrane, mitochondrial matrix, cytosol.

A number of CYPs take part in cholesterol biosynthesis and elimination, thus playing an important role in maintaining cholesterol homeostasis. Under normal physiological conditions, cholesterol intake (diet or synthesized de novo from acetyl CoA) equals cholesterol elimination (degraded to bile salts, secreted in bile and used in steroid hormone synthesis). These processes are under tight regulatory control and any disruption leads to increased cholesterol levels resulting in cardiovascular disease. The CYPs involved in cholesterol homeostasis could serve as potential targets for cholesterol-lowering drugs (Lewis 2004, Guengerich 2006, Pikuleva 2006).

References

Lewis DF (2004). 57 varieties: the human cytochromes P450. Pharmacogenomics, 5, 305-18.

Guengerich FP (2006). Cytochrome P450s and other enzymes in drug metabolism and toxicity. AAPS J, 8, E101-11.

Pikuleva IA (2006). Cytochrome P450s and cholesterol homeostasis. Pharmacol Ther, 112, 761-73.

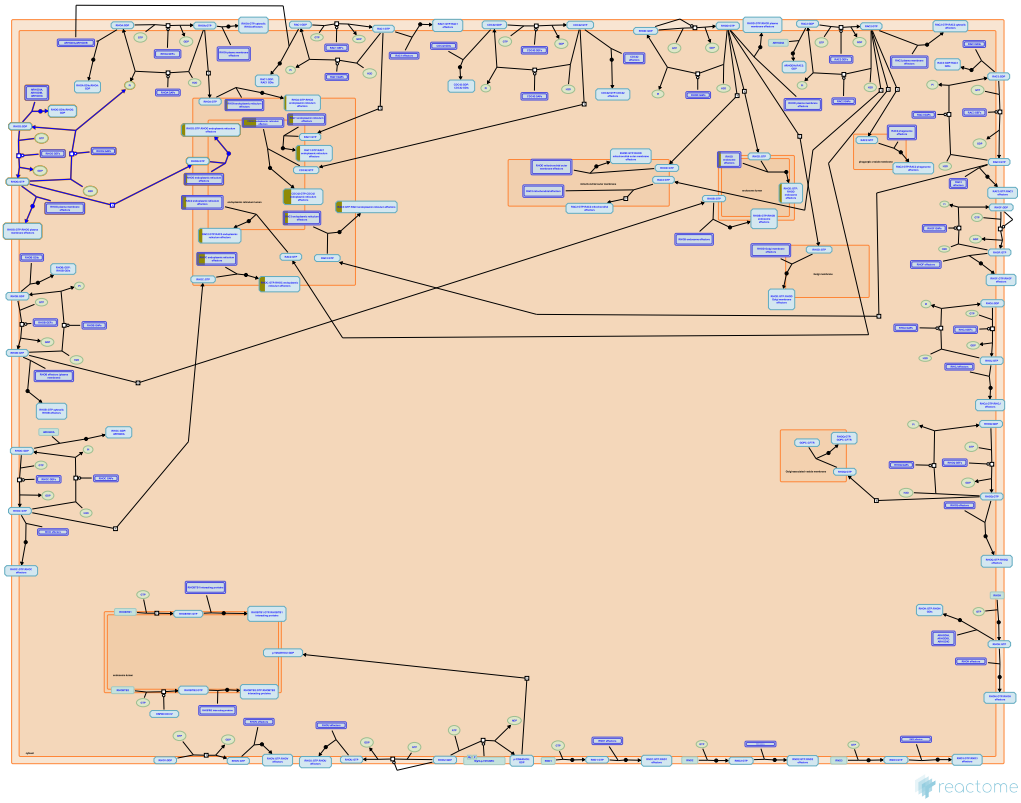
Edit history

Date	Action	Author
2008-02-08	Created	Jassal B
2008-05-19	Revised	Jassal B
2008-05-19	Edited	Jassal B
2008-05-19	Authored	Jassal B
2008-05-28	Reviewed	D'Eustachio P
2014-06-23	Revised	Jassal B
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
CYP51A1	Q16850

17. RHOG GTPase cycle (R-HSA-9013408)



This pathway catalogues RHOG guanine nucleotide exchange factors (GEFs), GTPase activator proteins (GAPs), GDP dissociation inhibitors (GDIs) and RHOG effectors. RHOG is a RAC-related RHO GTPase, ~70% identical to RAC1 (Vincent et al. 1992, de Curtis 2008). RHOG is broadly expressed in different tissue types. It regulates the cytoskeleton, acting either upstream of or in parallel to RAC1. RHOG regulates cell polarity, adhesion, migration and invasion, contributing to the formation of lamellipodia and invadopodia (Gauthier-Rouvière et al. 1998, Al-Koussa et al. 2020). The ortholog of RHOG is required for neuronal development in C. elegans (de Curtis 2008). RHOG is involved in VEGF signaling and angiogenesis (El Baba et al. 2020). RHOG cooperates with RAC1 and CDC42 in malignant cell transformation (Roux et al. 1997) and may contribute to invasiveness of cancer cells (Al-Koussa et al. 2020).

References

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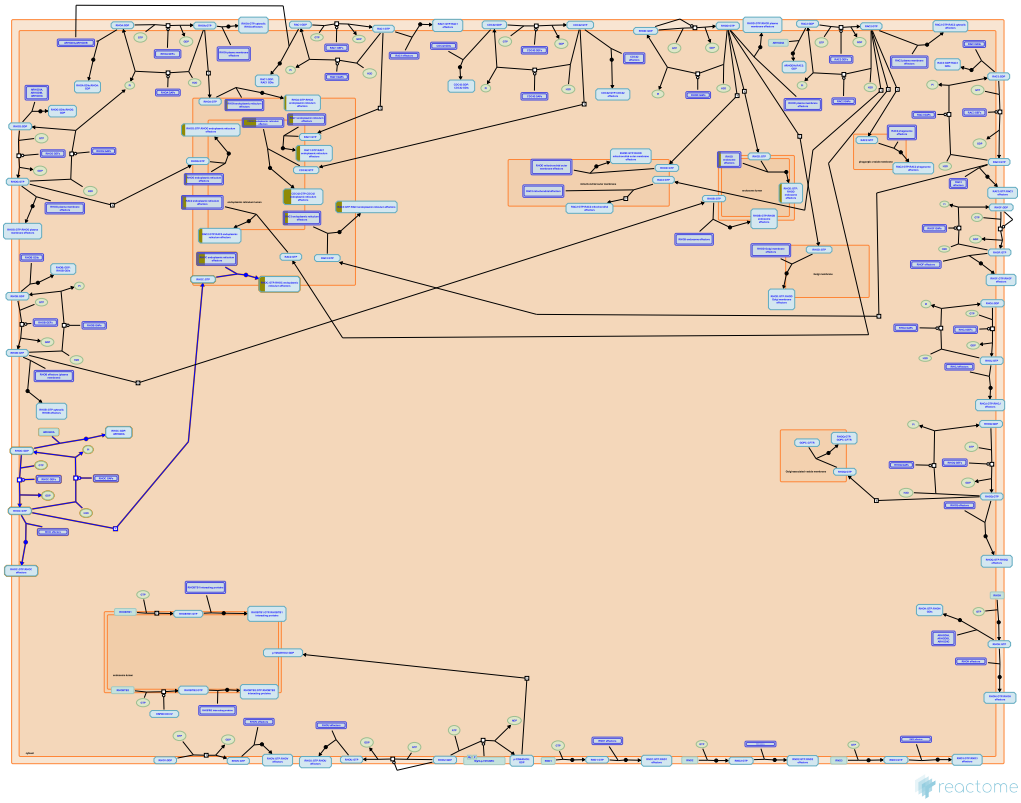
Edit history

Date	Action	Author
2017-07-24	Created	Orlic-Milacic M
2020-07-14	Authored	Orlic-Milacic M
2021-02-04	Reviewed	Fort P
2021-02-25	Edited	Orlic-Milacic M
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

18. RHOC GTPase cycle (R-HSA-9013106)



This pathway catalogues RHOC guanine nucleotide exchange factors (GEFs), GTPase activator proteins (GAPs), GDP dissociation inhibitors (GDIs) and RHOC effectors. RHOC belongs to the RHOA subfamily of RHO GTPases and shares 85% sequence identity with RHOA and RHOB (Wheeler and Ridley 2004). Like RHOA and RHOB, RHOC regulates the cytoskeleton and is involved in cell adhesion and migration (Guan et al. 2018). RHOC contributes to invasiveness and metastatic potential of cancer cells (Bravo-Cordero et al. 2014; Guan et al. 2018; Thomas et al. 2019).

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Edit history

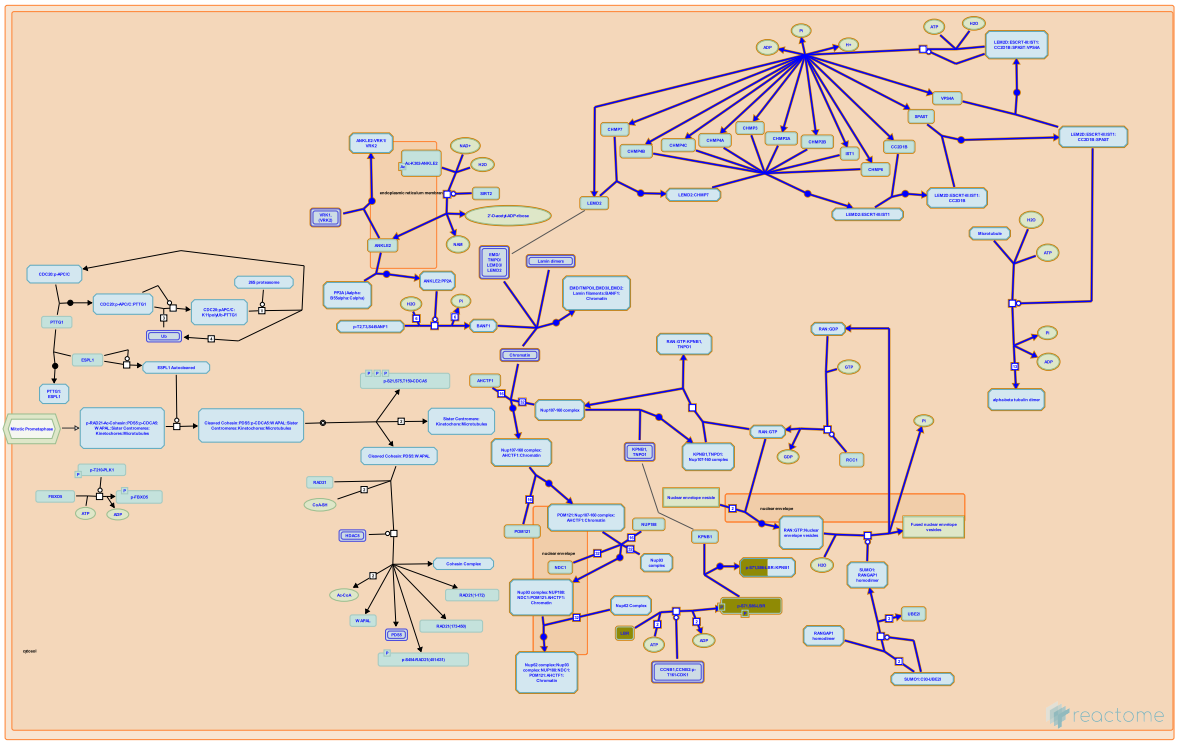
Date	Action	Author
2017-07-23	Created	Orlic-Milacic M
2020-07-14	Authored	Orlic-Milacic M
2021-02-04	Reviewed	Fort P

Date	Action	Author
2021-02-25	Edited	Orlic-Milacic M
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

19. Nuclear Envelope (NE) Reassembly (R-HSA-2995410)



Reassembly of the nuclear envelope (NE) around separated sister chromatids begins in late anaphase and is completed in telophase (reviewed by Wandke and Kutay 2013). Characteristic proteins of the inner nuclear membrane and nuclear lamina accumulate at the reforming NE (reviewed by Wandke and Kutay 2013). Concurrently, nuclear pore complexes (NPCs) assemble and insert into the reforming NE, and the NE becomes sealed to reestablish the nucleocytoplasmic diffusion barrier (reviewed by Otsuka and Ellenberg 2018).

References

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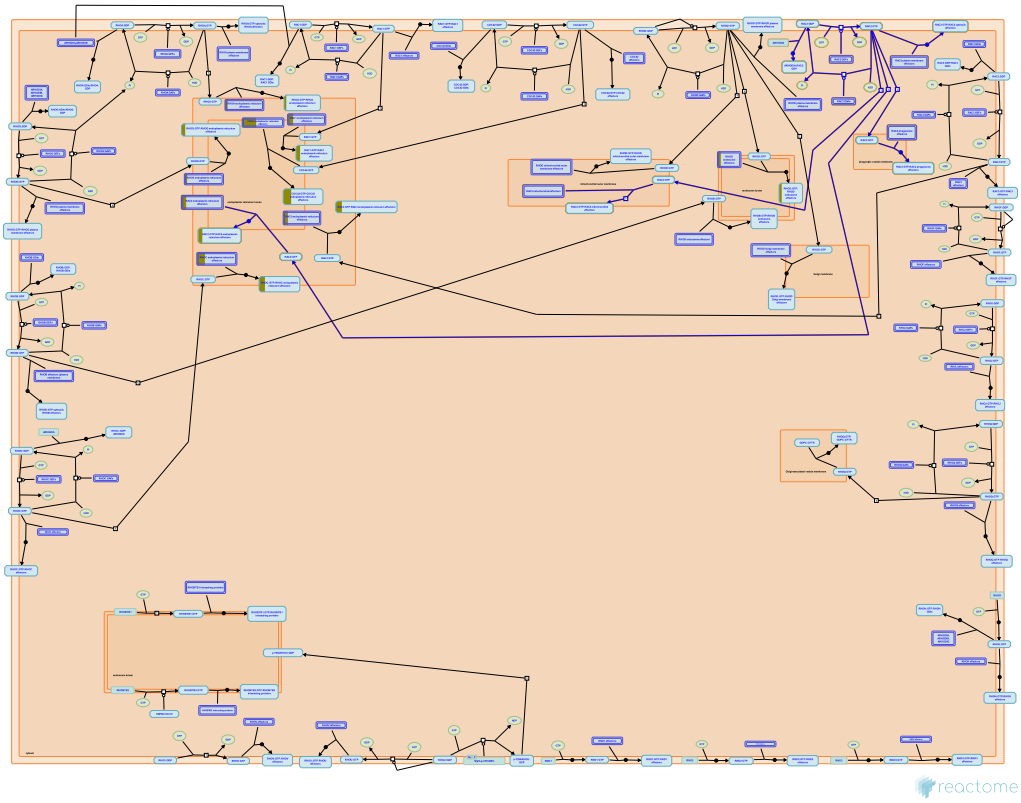
Edit history

Date	Action	Author
2013-01-22	Authored	Orlic-Milacic M
2013-01-22	Created	Orlic-Milacic M
2013-01-23	Edited	Gillespie ME
2019-11-06	Authored	Gerace L
2019-11-26	Edited	Orlic-Milacic M
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

20. RAC2 GTPase cycle (R-HSA-9013404)



This pathway catalogues RAC2 guanine nucleotide exchange factors (GEFs), GTPase activator proteins (GAPs), GDP dissociation inhibitors (GDIs) and RAC2 effectors. RAC2 is exclusively expressed in hematopoietic cells (Troeger and Williams 2013). RAC2 is a component of the phagocytic oxidase complex in neutrophils (Troeger and Williams 2013). RAC2 is required for adhesion and mobilization of hematopoietic stem cells and progenitor cells (Troeger and Williams 2013). RAC2 is also needed for adhesion, migration and degranulation of mast cells (Troeger and Williams 2013). Mutations in RAC2 have been found in a small number of patients with primary immunodeficiencies (Gu and Williams 2002; Troeger and Williams 2013; Lougaris et al. 2020).

References

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Edit history

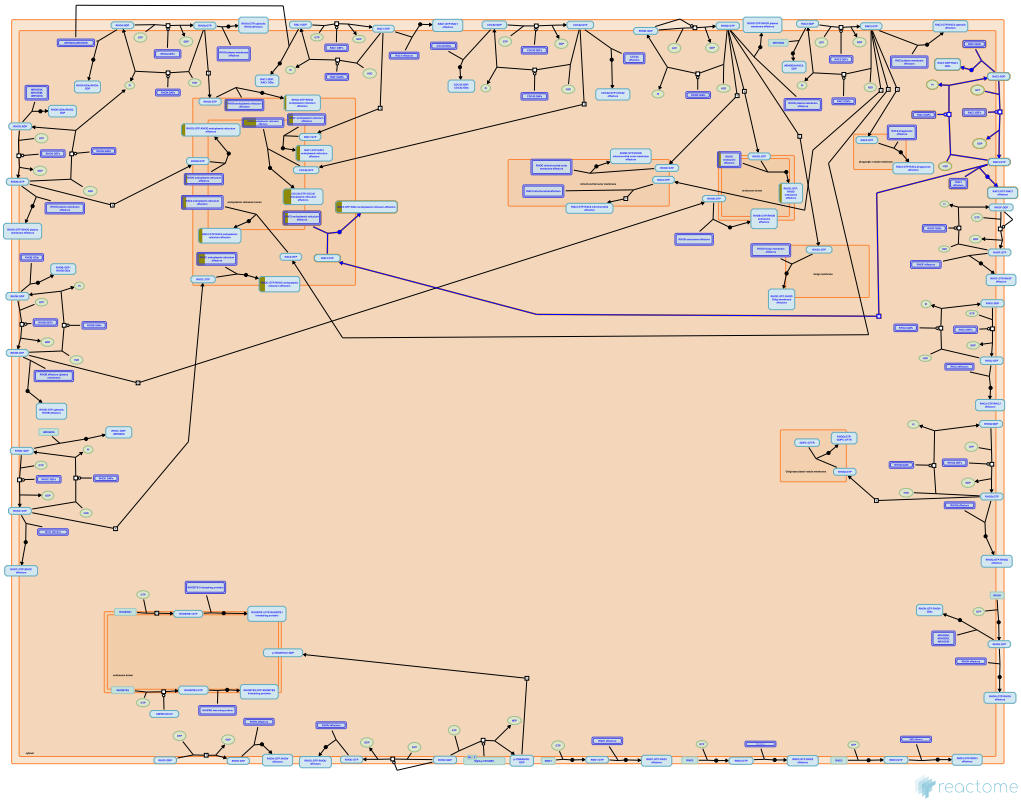
Date	Action	Author
2017-07-24	Created	Orlic-Milacic M
2020-07-13	Authored	Rothfels K
2020-07-14	Authored	Orlic-Milacic M
2021-02-04	Reviewed	Fort P

Date	Action	Author
2021-02-25	Edited	Orlic-Milacic M
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

21. RAC3 GTPase cycle (R-HSA-9013423)



This pathway catalogues RAC3 guanine nucleotide exchange factors (GEFs), GTPase activator proteins (GAPs), GDP dissociation inhibitors (GDIs) and RAC3 effectors. RAC3 is highly similar to RAC1 (92% amino acid sequence identity), but it is expressed in fewer tissues than RAC1. RAC3 orthologues only exist in vertebrates (de Curtis 2019). RAC3 is highly expressed in neurons and plays an important role in neuronal and brain development (de Curtis 2014, de Curtis 2019). RAC3 mutations have been reported in patients with intellectual disability and brain malformations (de Curtis 2019). RAC3 is frequently overexpressed in cancer and contributes to proliferation, migration and invasiveness of cancer cells (de Curtis 2019).

References

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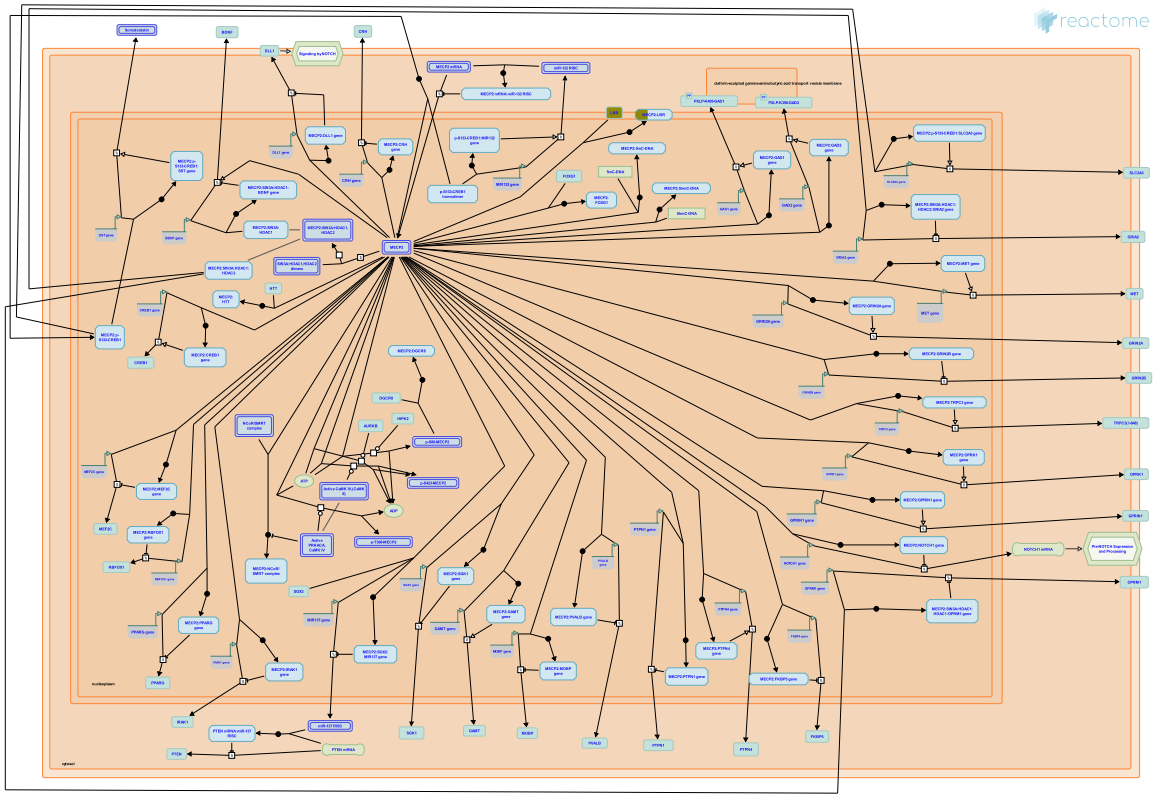
Edit history

Date	Action	Author
2017-07-24	Created	Orlic-Milacic M
2020-07-13	Authored	Rothfels K
2020-07-14	Authored	Orlic-Milacic M
2021-02-04	Reviewed	Fort P
2021-02-25	Edited	Orlic-Milacic M
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

22. Transcriptional Regulation by MECP2 (R-HSA-8986944)



MECP2 is an X chromosome gene whose loss-of-function mutations are an underlying cause of the majority of Rett syndrome cases. The MECP2 gene locus consists of four exons. Both exon 1 and exon 2 contain translation start sites. Alternative splicing of the second exon results in expression of two MECP2 transcript isoforms, MECP2_e1 (MECP2B or MECP2alpha) and MECP2_e2 (MECP2A or MECP2beta). The N-terminus of the MECP2_e1 isoform, in which exon 2 is spliced out, is encoded by exon 1. The N-terminus of the MECP2_e2 isoforms, which includes both exon 1 and exon 2, is encoded by exon 2, as the exon 2 translation start site is used. Exons 3 and 4 are present in both isoforms. The MECP2_e2 isoform was cloned first and is therefore more extensively studied. The MECP2_e1 isoform is more abundant in the brain (Mnatzakanian et al. 2004, Kriaucionis and Bird 2004, Kaddoum et al. 2013). Mecp2 isoforms show different expression patterns during mouse brain development and in adult brain regions (Dragich et al. 2007, Olson et al. 2014). While Rett syndrome mutations mainly occur in exons 3 and 4 of MECP2, thereby affecting both MECP2 isoforms (Mnatzakanian et al. 2004), some mutations occur in exon 1, affecting MECP2_e1 only. No mutations have been described in exon 2 (Gianakopoulos et al. 2012). Knockout of Mecp2_e1 isoform in mice, through a naturally occurring Rett syndrome point mutation which affects the first translation codon of MECP2_e1, recapitulates Rett-like phenotype. Knockout of Mecp2_e2 isoform in mice does not result in impairment of neurologic functions (Yasui et al. 2014). In Mecp2 null mice, transgenic expression of either Mecp2_e1 or Mecp2_e2 prevents development of Rett-like phenotype, with Mecp2_e1 rescuing more Rett-like symptoms than Mecp2_e2. This indicates that both splice variants can fulfill basic Mecp2 functions in the mouse brain (Kerr et al. 2012). Changes in gene expression upon over-expression of either MECP2_e1 or MECP2_e2 imply overlapping as well as distinct target genes (Orlic-Milacic et al. 2014).

Methyl-CpG-binding protein 2 encoded by the MECP2 gene binds to methylated CpG sequences in the DNA. The binding is not generic, however, but is affected by the underlying DNA sequence (Yoon et al. 2003). MECP2 binds to DNA containing 5 methylcytosine (5mC DNA), a DNA modification associated with transcriptional repression (Mellen et al. 2012), both in the context of CpG islands and outside of CpG islands (Chen et al. 2015). In addition, MECP2 binds to DNA containing 5 hydroxymethylcytosine (5hmC DNA), a DNA modification associated with transcriptional activation (Mellen et al. 2012). MECP2 binds to DNA as a monomer, occupying about 11 bp of the DNA. Binding of one MECP2 molecule facilitates binding of the second MECP2 molecule, and therefore clustering can occur at target sites. MECP2 binding to chromatin may be facilitated by nucleosome methylation (Ghosh et al. 2010).

MECP2 was initially proposed to act as a generic repressor of gene transcription. However, high throughput studies of MECP2-induced changes in gene expression in mouse hippocampus (Chahrour et al. 2008), and mouse and human cell lines (Orlic-Milacic et al. 2014) indicate that more genes are up-regulated than down-regulated when MECP2 is overexpressed. At least for some genes directly upregulated by MECP2, it was shown that a complex of MECP2 and CREB1 was involved in transcriptional stimulation (Chahrour et al. 2008, Chen et al. 2013).

MECP2 expression is the highest in postmitotic neurons compared to other cell types, with MECP2 being almost as abundant as core histones. Phosphorylation of MECP2 in response to neuronal activity regulates binding of MECP2 to DNA, suggesting that MECP2 may remodel chromatin in a neuronal activity-dependent manner. The resulting changes in gene expression would then modulate synaptic plasticity and behavior (reviewed by Ebert and Greenberg 2013). In human embryonic stem cell derived Rett syndrome neurons, loss of MECP2 is associated with a significant reduction in transcription of neuronally active genes, as well as the reduction in nascent protein synthesis. The reduction in nascent protein synthesis can at least in part be attributed to the decreased activity of the PI3K/AKT/mTOR signaling pathway. Neuronal morphology (reduced soma size) and the level of protein synthesis in Rett neurons can be ameliorated by treating the cells with growth factors which activate the PI3K/AKT/mTOR cascade or by inhibition of PTEN, the negative regulator of AKT activation. Mitochondrial gene expression is also downregulated in Rett neurons, which is associated with a reduced capacity of the mitochondrial electron transport chain (Ricciardi et al. 2011, Li et al. 2013). Treatment of Mecp2 null mice with IGF1 (insulin-like growth factor 1) reverses or ameliorates some Rett-like features such as locomotion, respiratory difficulties and irregular heart rate (Tropea et al. 2009).

MECP2 regulates expression of a number of ligands and receptors involved in neuronal development and function. Ligands regulated by MECP2 include BDNF (reviewed by Li and Pozzo-Miller 2014, and KhorshidAhmad et al. 2016), CRH (McGill et al. 2006, Samaco et al. 2012), SST (Somatostatin) (Chahrour et al. 2008), and DLL1 (Li et al. 2014). MECP2 also regulates transcription of genes involved in the synthesis of the neurotransmitter GABA – GAD1 (Chao et al. 2010) and GAD2 (Chao et al. 2010, He et al. 2014). MECP2 may be involved in direct stimulation of transcription from the GLUD1 gene promoter, encoding mitochondrial glutamate dehydrogenase 1, which may be involved in the turnover of the neurotransmitter glutamate (Livide et al. 2015). Receptors regulated by MECP2 include glutamate receptor GRIA2 (Qiu et al. 2012), NMDA receptor subunits GRIN2A (Durand et al. 2012) and GRIN2B (Lee et al. 2008), opioid receptors OPRK1 (Chahrour et al. 2008) and OPRM1 (Hwang et al. 2009, Hwang et al. 2010, Samaco et al. 2012), GPRIN1 (Chahrour et al. 2008), MET (Plummer et al. 2013), NOTCH1 (Li et al. 2014). Channels/transporters regulated by MECP2 include TRPC3 (Li et al. 2012) and SLC2A3 (Chen et al. 2013). MECP2 regulates transcription of FKBP5, involved in trafficking of glucocorticoid receptors (Nuber et al. 2005, Urdinguio et al. 2008). MECP2 is implicated in regulation of expression of SEMA3F (semaphorin 3F) in mouse olfactory neurons (Degano et al. 2009). In zebrafish, Mecp2 is implicated in sensory axon guidance by direct stimulation of transcription of Sema5b and Robo2 (Leong et al. 2015). MECP2 may indirectly regulate signaling by neuronal receptor tyrosine kinases by regulating transcription of protein tyrosine phosphatases, PTPN1 (Krishnan et al. 2015) and PTPN4 (Williamson et al. 2015).

MECP2 regulates transcription of several transcription factors involved in functioning of the nervous system, such as CREB1, MEF2C, RBFOX1 (Chahrour et al. 2008) and PPARG (Mann et al. 2010, Joss-Moore et al. 2011).

MECP2 associates with transcription and chromatin remodeling factors, such as CREB1 (Chahrour et al. 2008, Chen et al. 2013), the HDAC1/2-containing SIN3A co-repressor complex (Nan et al. 1998), and the NCoR/SMRT complex (Lyst et al. 2013, Ebert et al. 2013). There are contradictory reports on the interaction of MECP2 with the SWI/SNF chromatin-remodeling complex (Harikrishnan et al. 2005, Hu et al. 2006). Interaction of MECP2 with the DNA methyltransferase DNMT1 has been reported, with a concomitant increase in enzymatic activity of DNMT1 (Kimura and Shiota 2003).

In addition to DNA binding-dependent regulation of gene expression by MECP2, MECP2 may influence gene expression by interaction with components of the DROSHA microprocessor complex and the consequent change in the levels of mature microRNAs (Cheng et al. 2014, Tsujimura et al. 2015).

Increased MECP2 promoter methylation is observed in both male and female autism patients (Nagarajan et al. 2008). Regulatory elements that undergo methylation are found in the promoter and the first intron of MECP2 and their methylation was shown to regulate Mecp2 expression in mice (Liyanage et al. 2013). Mouse Mecp2 promoter methylation was shown to be affected by stress (Franklin et al. 2010).

The Rett-like phenotype of Mecp2 null mice is reversible (Guy et al. 2007), but appropriate levels of Mecp2 expression need to be achieved (Alvarez-Saavedra et al. 2007). When Mecp2 expression is restored in astrocytes of Mecp2 null mice, amelioration of Rett symptoms occurs, involving non-cell-autonomous positive effect on mutant neurons and increasing level of the excitatory glutamate transporter VGLUT1 (Lioy et al. 2011). Microglia derived from Mecp2 null mice releases higher than normal levels of glutamate, which has toxic effect on neurons. Increased glutamate secretion may be due to increased levels of glutaminase (Gls), involved in glutamate synthesis, and increased levels of connexin-32 (Gjb1), involved in glutamate release, in Mecp2 null microglia (Maezawa and Jin 2010). Targeted deletion of Mecp2 from Sim1-expressing neurons of the mouse hypothalamus recapitulates some Rett syndrome-like features and highlights the role of Mecp2 in feeding behavior and response to stress (Fyffe et al. 2008).

Mecp2 overexpression, similar to MECP2 duplication syndrome, causes neurologic phenotype similar to Rett (Collins et al. 2004, Luikenhuis et al. 2004, Van Esch et al. 2005, Alvarez-Saavedra 2007, Van Esch et al. 2012). The phenotype of the mouse model of the MECP2 duplication syndrome in adult mice is reversible when Mecp2 expression levels are corrected (Sztainberg et al. 2015).

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Dewell S, Heintz N, Mellén M, Kriaucionis S & Ayata P (2012). MeCP2 binds to 5hmC enriched within active genes and accessible chromatin in the nervous system. Cell, 151, 1417-30.

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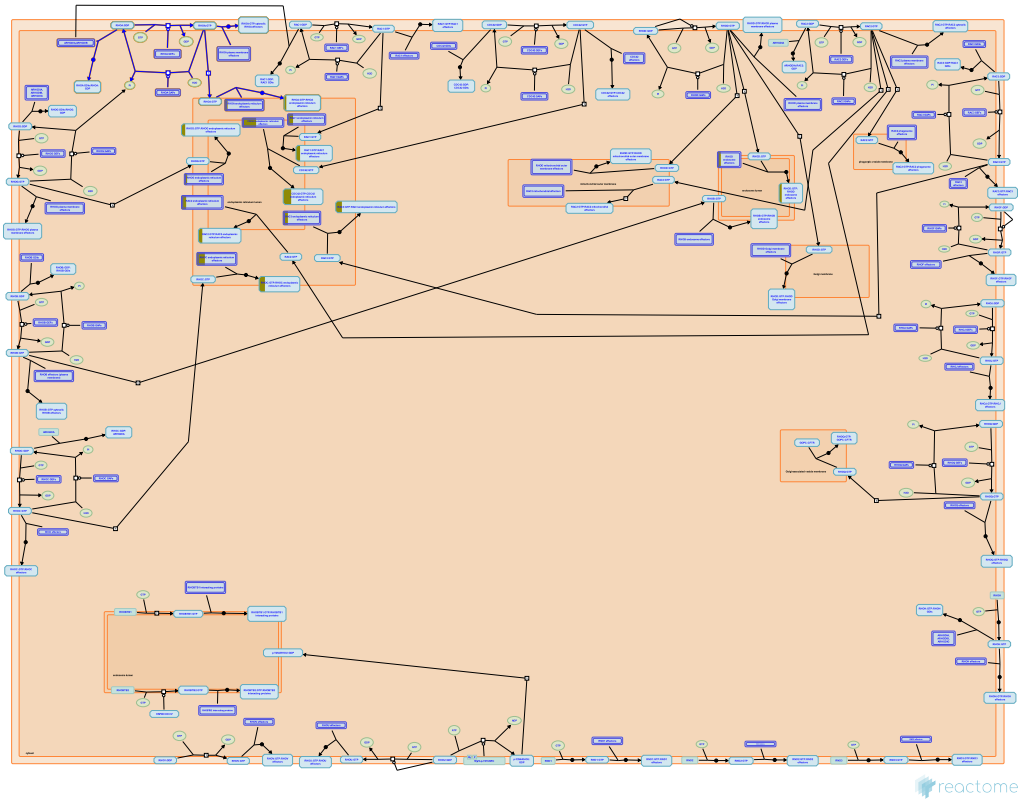
Edit history

Date	Action	Author
2017-05-05	Created	Orlic-Milacic M
2017-10-02	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2022-03-22	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

23. RHOA GTPase cycle (R-HSA-8980692)



This pathway catalogues RHOA guanine nucleotide exchange factors (GEFs), GTPase activator proteins (GAPs), GDP dissociation inhibitors (GDIs) and RHOA effectors. RHOA is one of the three best characterized RHO GTPases, the other two being RAC1 and CDC42, and is the founding member of the RHO GTPase family (Zhou and Zheng 2013). RHOA regulates the cytoskeleton and cell contractility (Lessey et al. 2012), thus playing a role in a number of cellular functions, such as adhesion, migration, survival, division, vesicle trafficking and gene expression (Zhou and Zheng 2013). RHOA-regulated processes are involved in mechanotransduction (Lessey et al. 2012; Marjoram et al. 2014), neuronal development (Zhou and Zheng 2013; Fujita and Yamashita 2014; Hu and Selzer 2017), immune system development (Zhou and Zheng 2013; Ricker et al. 2016; Bros et al. 2019), and cardiovascular regulation (Zhou and Zheng 2013; Cai et al. 2016; Shimokawa et al. 2016). RHOA mutations are frequently found in cancer (Kataoka and Ogawa 2016). Toxins of numerous pathogens target RHOA to hijack the host cytoskeleton (Jamilloux et al. 2018).

References

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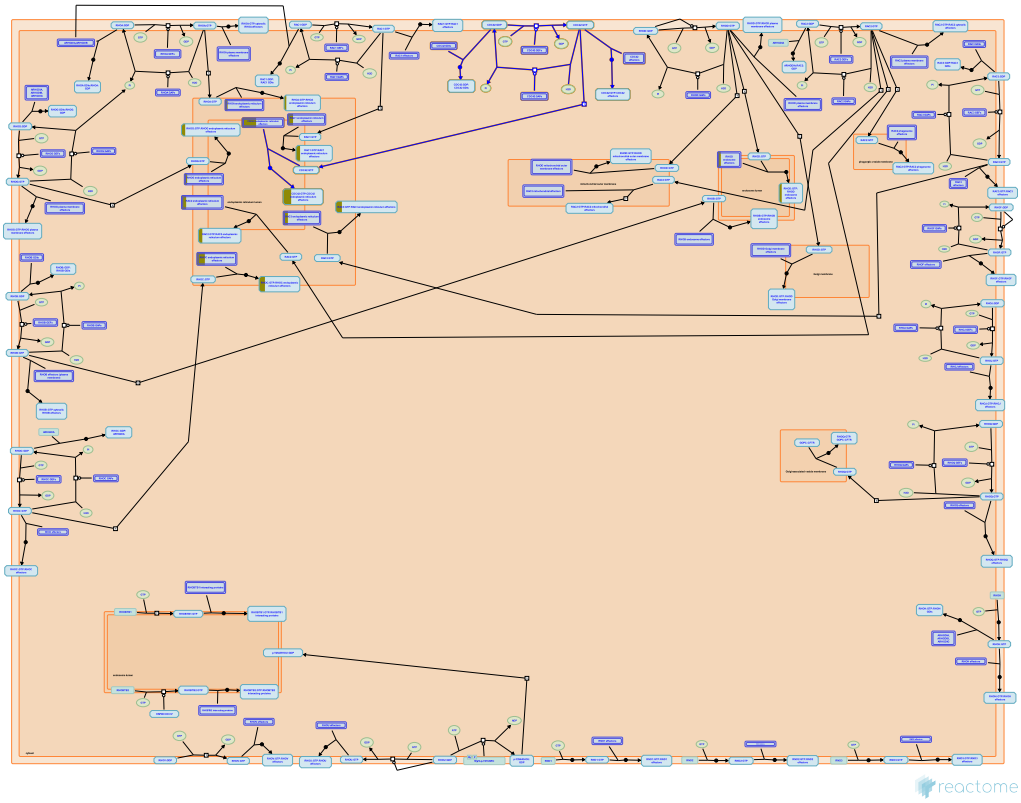
Edit history

Date	Action	Author
2017-02-28	Created	Orlic-Milacic M
2020-07-14	Authored	Orlic-Milacic M
2021-02-04	Reviewed	Fort P
2021-02-25	Edited	Orlic-Milacic M
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

24. CDC42 GTPase cycle (R-HSA-9013148)



This pathway catalogues CDC42 guanine nucleotide exchange factors (GEFs), GTPase activator proteins (GAPs), GDP dissociation inhibitors (GDIs) and CDC42 effectors. CDC42 is one of the three best characterized RHO GTPases, the other two being RHOA and RAC1. By regulating the cytoskeleton, CDC42 regulates cell polarity across different species, from yeast to humans (Pichaud et al. 2019, Woods and Lew 2019). CDC42 is an essential regulator of polarized morphogenesis in epithelial cells, where it coordinates formation of the apical membrane and lumen formation, as well as junction maturation (Pichaud et al. 2019). CDC42 plays a role in cell-to-cell adhesion and cell cycle regulation (Xiao et al. 2018). CDC42 takes part in the regulation of membrane trafficking. Dysfunction of several CDC42-specific GEFs has been shown to impair intracellular trafficking (Egorov and Polishchuk 2017). CDC42 participates in insulin synthesis and secretion and contributes to the pathogenesis of insulin resistance and diabetic nephropathy (Huang et al. 2019). CDC42 is often dysregulated in cancer because a number of GEFs and GEF activators that act upstream of RAC1 and CDC42 are known oncogenes (Aguilar et al. 2017; Maldonado et al. 2018; Zhang et al. 2019; Maldonado et al. 2020). CDC4 promotes cancer cell proliferation, survival, invasion, migration and metastasis (Xiao et al. 2018), especially under hyperglycemia (Huang et al. 2019).

References

Duan J, Li J, Xiao XH, Huang QY, Lv LC, Qian XL, ... Lai XN (2019). Cdc42: A Novel Regulator of Insulin Secretion and Diabetes-Associated Diseases. Int J Mol Sci, 20.

Lew DJ & Woods B (2019). Polarity establishment by Cdc42: Key roles for positive feedback and differential mobility. Small GTPases, 10, 130-137.

Pichaud F, Nunes de Almeida F & Walther RF (2019). Regulation of Cdc42 and its effectors in epithelial morphogenesis. J. Cell. Sci., 132.

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Duan J, Xiao XH, Lv LC, Xiong LX, Wu YM, He SJ & Hu ZZ (2018). Regulating Cdc42 and Its Signaling Pathways in Cancer: Small Molecules and MicroRNA as New Treatment Candidates. Molecules, 23.

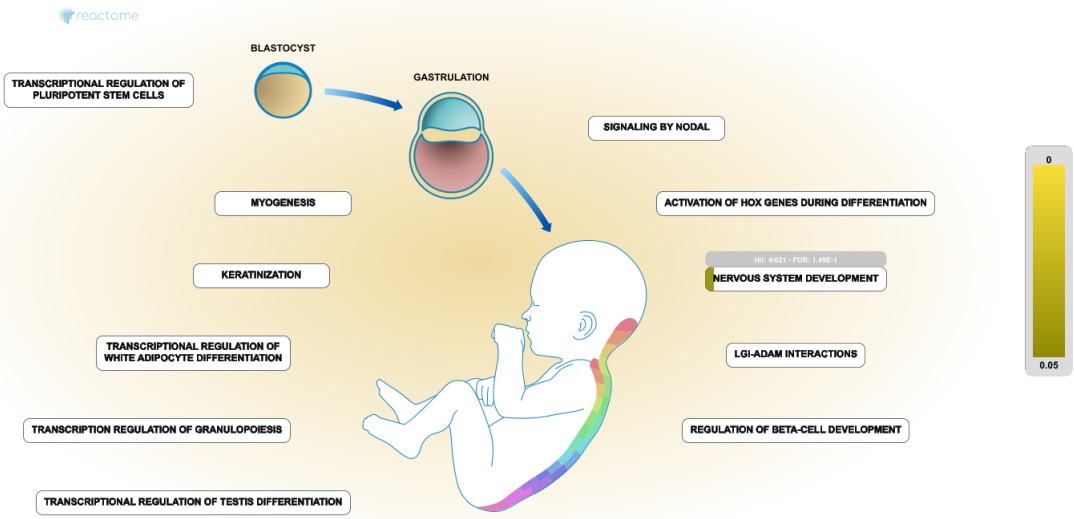
Edit history

Date	Action	Author
2017-07-24	Created	Orlic-Milacic M
2020-07-13	Authored	Rothfels K
2020-07-14	Authored	Orlic-Milacic M
2021-02-04	Reviewed	Fort P
2021-02-25	Edited	Orlic-Milacic M
2021-05-16	Reviewed	Das ME
2021-06-10	Revised	Orlic-Milacic M
2021-06-10	Edited	Orlic-Milacic M
2022-03-23	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
LBR	Q14739

25. Developmental Biology (R-HSA-1266738)



As early steps towards capturing the array of processes by which a fertilized egg gives rise to the diverse tissues of the body, examples of eleven processes have been annotated. Aspects of two processes involved in most developmental processes, **transcriptional regulation of pluripotent stem cells**, and **activation of HOX genes during differentiation** are annotated. More specialized processes include **nervous system development** , aspects of the roles of cell adhesion molecules in **axonal guidance** and **myogenesis**, of **transcriptional regulation in pancreatic beta cell**, **transcriptional regulation of granulopoeisis**, and **transcriptional regulation of white adipocyte differentiation**, molecular events of **"nodal" signaling**, **LGI-ADAM interactions**, **keratinization**, and <b>transcriptional regulation of testis differentiation.

References

Edit history

Date	Action	Author
2011-05-06	Edited	Matthews L
2011-05-06	Created	Orlic-Milacic M
2011-08-22	Reviewed	Jensen J, Walmod PS, Maness PF, Krauss RS
2022-03-23	Modified	Weiser JD

2 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id	Input	UniProt Id
CYP51A1	Q16850	HMGCR	P04035

Input	Ensembl Id	Input	Ensembl Id
CYP51A1	ENSG00000001630	HMGCR	ENSG00000113161

6. Identifiers found

Below is a list of the input identifiers that have been found or mapped to an equivalent element in Reactome, classified by resource.

18 of the submitted entities were found, mapping to 31 Reactome entities

Input	UniProt Id
CYP51A1	Q16850
EBP	Q15125
HSD17B7	P56937
LBR	O76062, Q14739
MVK	Q03426
SC5D	O75845

Input	UniProt Id
DHCR24	Q15392
FDFT1	P37268
IDI1	Q13907
LSS	P48449
NSDHL	Q15738
SQLE	Q14534

Input	UniProt Id
DHCR7	Q9UBM7
HMGCR	P04035-1, P04035-2
IDI2	Q13907, Q9BXS1
MSMO1	Q15800
PMVK	Q15126
TM7SF2	O76062

Input	Ensembl Id
CYP51A1	ENSG00000001630
HMGCR	ENSG00000113161
MVK	ENSG00000110921
SQLE	ENSG00000104549

Input	Ensembl Id
DHCR7	ENSG00000172893
IDI1	ENSG00000067064
PMVK	ENSG00000163344
TM7SF2	ENSG00000149809

Input	Ensembl Id
FDFT1	ENSG00000079459
LSS	ENSG00000160285
SC5D	ENSG00000109929

7. Identifiers not found

These 3 identifiers were not found neither mapped to any entity in Reactome.

FAXDC2 MAGEA2 MAGEA2B