



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 78 on 02/12/2021. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTEyMDIxNTQ3NDhfMTAzMjA%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
2. Properties
3. Genome-wide overview
4. Most significant pathways
5. Pathways details
6. Identifiers found
7. Identifiers not found

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:

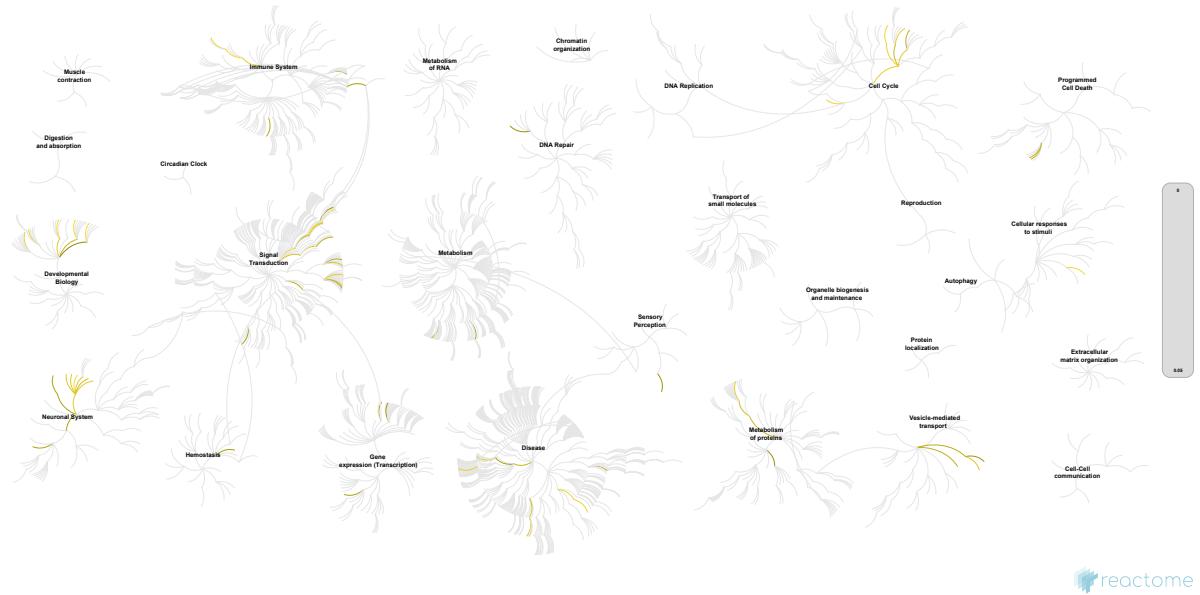
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 62 out of 81 identifiers in the sample were found in Reactome, where 626 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 'UniProt'.
- The unique ID for this analysis (token) is MjAyMTEyMDIxNTQ3NDhfMTAzMjA%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.

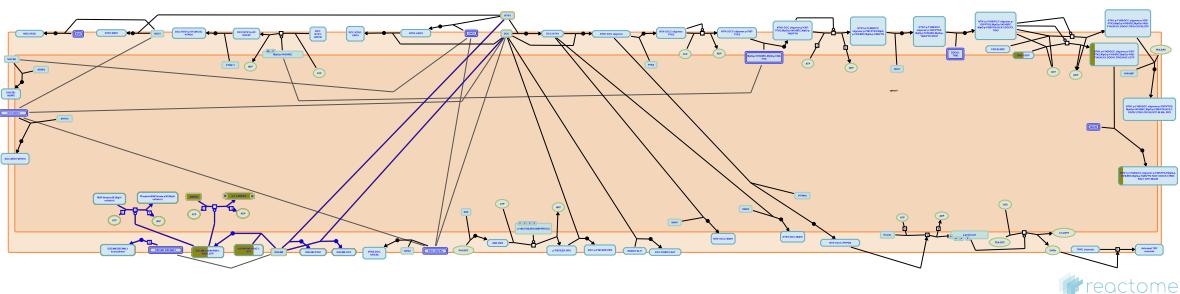
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
DSCAM interactions	3 / 11	9.79e-04	1.41e-04	0.099	3 / 6	4.42e-04
Toxicity of botulinum toxin type G (botG)	2 / 4	3.56e-04	6.13e-04	0.133	4 / 5	3.68e-04
Ephrin signaling	3 / 19	0.002	6.91e-04	0.133	11 / 11	8.10e-04
Signal transduction by L1	3 / 21	0.002	9.22e-04	0.133	3 / 11	8.10e-04
NTRK2 activates RAC1	2 / 5	4.45e-04	9.52e-04	0.133	2 / 2	1.47e-04
Glutamate Neurotransmitter Release Cycle	3 / 24	0.002	0.001	0.135	4 / 8	5.89e-04
Activated NTRK2 signals through CDK5	2 / 6	5.34e-04	0.001	0.135	6 / 6	4.42e-04
Amino acids regulate mTORC1	4 / 55	0.005	0.002	0.135	12 / 12	8.84e-04
Activated NTRK2 signals through FYN	2 / 7	6.23e-04	0.002	0.144	7 / 7	5.16e-04
Toxicity of botulinum toxin type B (botB)	2 / 8	7.12e-04	0.002	0.168	4 / 5	3.68e-04
CD28 co-stimulation	3 / 33	0.003	0.003	0.192	4 / 19	0.001
Cohesin Loading onto Chromatin	2 / 10	8.90e-04	0.004	0.192	2 / 2	1.47e-04
Establishment of Sister Chromatid Cohesion	2 / 11	9.79e-04	0.004	0.192	4 / 4	2.95e-04
Killing mechanisms	2 / 12	0.001	0.005	0.192	6 / 9	6.63e-04
WNT5:FZD7-mediated leishmania damping	2 / 12	0.001	0.005	0.192	6 / 9	6.63e-04
CD28 dependent Vav1 pathway	2 / 12	0.001	0.005	0.192	2 / 6	4.42e-04
SUMOylation of DNA damage response and repair proteins	4 / 81	0.007	0.006	0.192	3 / 24	0.002
Activation of RAC1	2 / 13	0.001	0.006	0.192	2 / 4	2.95e-04
Mitotic Telophase/Cytokinesis	2 / 13	0.001	0.006	0.192	2 / 4	2.95e-04
Condensation of Prophase Chromosomes	3 / 45	0.004	0.008	0.192	3 / 10	7.37e-04
Costimulation by the CD28 family	4 / 88	0.008	0.008	0.192	9 / 35	0.003
Signaling by NTRKs	5 / 139	0.012	0.008	0.192	47 / 164	0.012
M Phase	9 / 393	0.035	0.009	0.192	24 / 91	0.007
MPS IIIA - Sanfilippo syndrome A	1 / 1	8.90e-05	0.009	0.192	2 / 2	1.47e-04
Defective CYP27A1 causes CTX	1 / 1	8.90e-05	0.009	0.192	2 / 2	1.47e-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. DSCAM interactions (R-HSA-376172)



Cellular compartments: plasma membrane.

DSCAM (Down syndrome cell adhesion molecule) is one of the members of the Ig superfamily CAMs with a domain architecture comprising 10 Ig domains, 6 fibronectin type III (FN) repeats, a single transmembrane and a C terminal cytoplasmic domain. DSCAM is implicated in Down syndrome (DS) due to the chromosomal location of the DSCAM gene, but no evidence supports a direct involvement of DSCAM with DS. It likely functions as a cell surface receptor mediating axon pathfinding. Besides these important implications, little is known about the physiological function or the molecular mechanism of DSCAM signal transduction in mammalian systems. A closely related DSCAM parologue Down syndrome cell adhesion moleculelike protein 1 (DSCAML1) is present in humans. Both these proteins are involved in homophilic intercellular interactions.

References

- Nikolaev A, Ly A, Stein E, Zheng Y, Tessier-Lavigne M & Suresh G (2008). DSCAM is a netrin receptor that collaborates with DCC in mediating turning responses to netrin-1. *Cell*, 133, 1241-54. [🔗](#)
- Agarwala KL, Yamakawa K, Tsutsumi Y & Nakamura S (2000). Down syndrome cell adhesion molecule DSCAM mediates homophilic intercellular adhesion. *Brain Res Mol Brain Res*, 79, 118-26. [🔗](#)

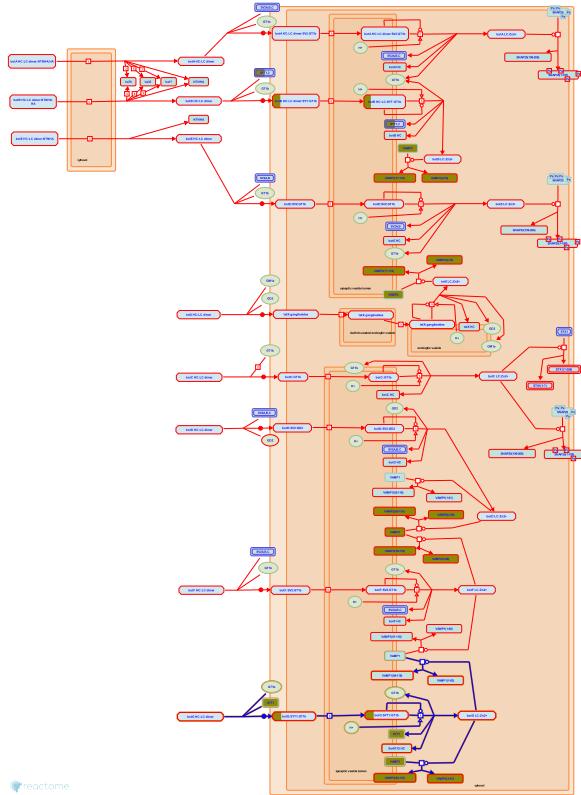
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2010-01-05	Edited	Garapati P V
2010-01-05	Authored	Garapati P V
2010-08-10	Reviewed	Clemens JC
2021-09-10	Modified	Weiser JD

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1496	P45983	5058	Q13153	5879	P63000

2. Toxicity of botulinum toxin type G (botG) (R-HSA-5250989)



Diseases: botulism.

Botulinum toxin type G (botG) is rarely if ever associated with human disease (Hatheway 1995) and a pathway by which it might enter the circulation from the human gut has not been described. Nevertheless, the toxin itself, a disulfide-bonded heavy chain (HC) - light chain (LC) heterodimer ("di-chain"), is capable of binding to neurons by interactions with cell-surface ganglioside and syntagmin 1 (SYT1) (Peng et al. 2012; Willjes et al. 2013), the bound toxin can enter synaptic vesicles and release its LC moiety into the cytosol of targeted cells (Montal 2010), and the botG LC can cleave vesicle-associated membrane proteins 1 and 2 (VAMP1 and 2) on the cytosolic face of the synaptic vesicle membrane (Schiavo et al. 1994; Yamasaki et al. 1994). These four events are annotated here.

References

- Mahrhold S, Strotmeier J, Rummel A, Eichner T, Binz T & Willjes G (2013). Botulinum neurotoxin G binds synaptotagmin-II in a mode similar to that of serotype B: tyrosine 1186 and lysine 1191 cause its lower affinity. *Biochemistry*, 52, 3930-8. [🔗](#)
- Hayashi T, Yamasaki S, Niemann H, Eklund M, Szabo E, Binz T, ... Yamasaki N (1994). Botulinum neurotoxin type G proteolyses the Ala81-Ala82 bond of rat synaptobrevin 2. *Biochem. Biophys. Res. Commun.*, 200, 829-35. [🔗](#)
- Pitkin RM, Tepp WH, Berntsson RP, Stenmark P, Dong M, Peng L & Johnson EA (2012). Botulinum neurotoxin D-C uses synaptotagmin I and II as receptors, and human synaptotagmin II is not an effective receptor for type B, D-C and G toxins. *J. Cell. Sci.*, 125, 3233-42. [🔗](#)
- Montal M (2010). Botulinum neurotoxin: a marvel of protein design. *Annu. Rev. Biochem.*, 79, 591-617. [🔗](#)

Malizio C, Polverino de Laureto P, Trimble WS, Schiavo G, Milan G, Montecucco C, ... Sugiyama H (1994). Botulinum G neurotoxin cleaves VAMP/synaptobrevin at a single Ala-Ala peptide bond. J. Biol. Chem., 269, 20213-6. [🔗](#)

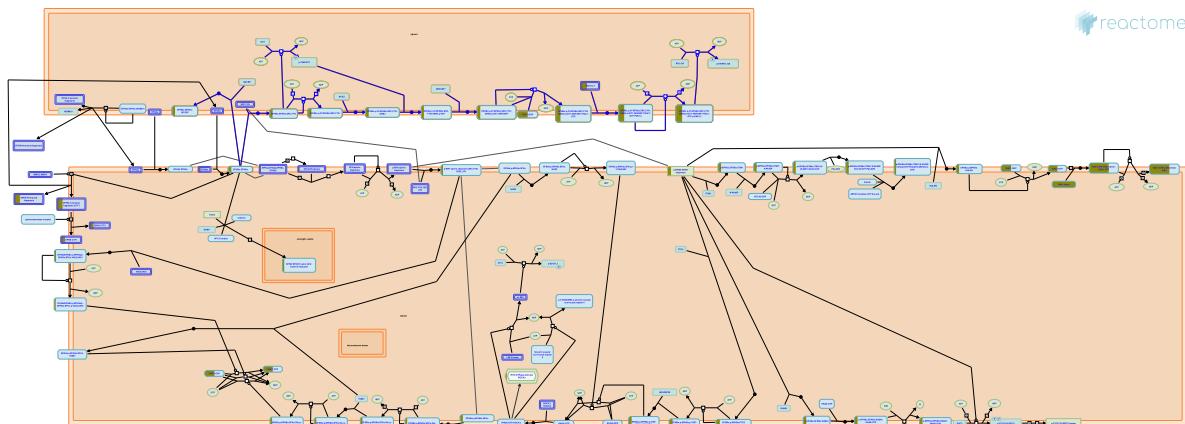
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Date	Action	Author
2006-06-15	Authored	Krupa S, Gopinathrao G
2007-08-03	Reviewed	Ichtchenko K
2014-02-01	Created	D'Eustachio P
2014-02-11	Revised	D'Eustachio P
2014-02-11	Edited	D'Eustachio P
2014-11-18	Reviewed	Sharma S, Thirunavukkarasu N
2020-10-08	Modified	D'Eustachio P

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

Input	UniProt Id	Input	UniProt Id
6844	P63027	6857	P21579

3. Ephrin signaling (R-HSA-3928664)



Cellular compartments: plasma membrane, cytosol.

The interaction between ephrin (EFN) ligands and EPH receptors results not only in forward signaling through the EPH receptor, but also in 'reverse' signaling through the EFN ligand itself. Reverse signaling through EFNB is required for correct spine morphogenesis and proper path-finding of corpus callosum and dorsal retinal axons. The molecular mechanism by which EFNBs transduce a reverse signal involves phosphorylation of multiple, conserved tyrosines on the intracellular domain of B-type ephrins, facilitating binding of the SH2/S3 domain adaptor protein GRB4 and subsequent cytoskeletal remodeling (Bruckner et al. 1997, Cowan & Henkemeyer 2001, Lu et al. 2001). The other mechanism of reverse signaling involves the C-terminus PSD-95/Dlg/ZO-1 (PDZ)-binding motif of EFNBs which recruits various PDZ domain containing proteins. Phosphorylation and PDZ-dependent reverse signaling by ephrin-B1 have each been proposed to play important roles in multiple contexts in development and disease (Bush & Soriano 2009).

References

Soriano P & Bush JO (2009). Ephrin-B1 regulates axon guidance by reverse signaling through a PDZ-dependent mechanism. *Genes Dev.*, 23, 1586-99. [View](#)

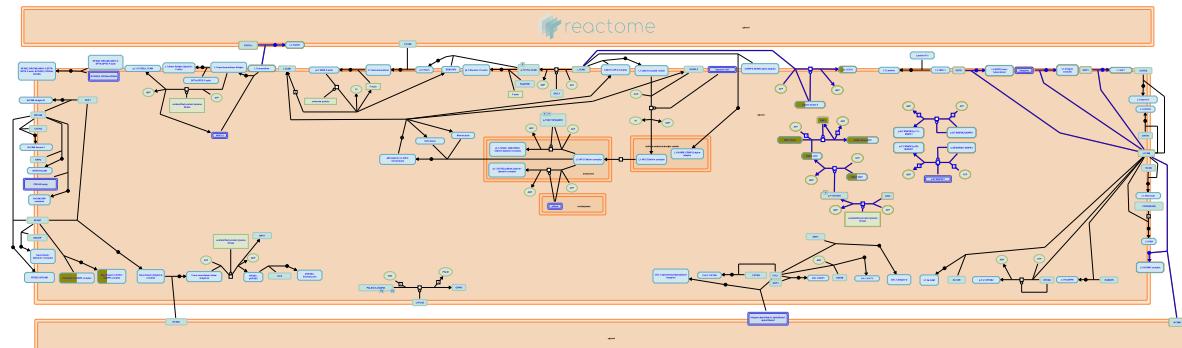
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2013-07-23	Authored	Garapati P V
2013-07-23	Created	Garapati P V
2014-05-19	Reviewed	Ip NY
2021-09-10	Modified	Weiser JD

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
2556	P54762	5058	Q13153	5879	P63000

4. Signal transduction by L1 (R-HSA-445144)



Besides adhesive roles in cell-cell interaction, L1 functions as a signal transducing receptor providing neurons with cues from their environment for axonal growth and guidance. L1 associates with beta1 integrins on the cell surface to induce a signaling pathway involving sequential activation of pp60csrc, Vav2-GEF, Rac1, PAK1, MEK and ERK1/2. L1 stimulates cell migration and neurite outgrowth through the MAP kinases ERK1/2. CHL1 also associates with integrins and activates a MAPK signaling pathway via pp60csrc, MEK and ERK1/2.

L1 also binds the Sema3A receptor neuropilin1 and acts as an obligate coreceptor to mediate Sema3A induced growth cone collapse and axon repulsion. This repulsion can be converted to attraction by homophilic binding of L1 on an apposing cell in trans with L1 complexed with Neuropilin1 (NP1) in the responding neuron.

L1 also interacts with FGF receptor and activates PLC gamma and DAG, resulting in the production of arachidonic acid and subsequent opening of voltage-gated channels.

References

- Schmid RS, Pruitt WM & Maness PF (2000). A MAP kinase-signaling pathway mediates neurite outgrowth on L1 and requires Src-dependent endocytosis. *J Neurosci*, 20, 4177-88. [🔗](#)
- Landreth G, Schaefer AW, Beach CM, Kamiguchi H, Lemmon V & Wong EV (1999). Activation of the MAPK signal cascade by the neural cell adhesion molecule L1 requires L1 internalization. *J Biol Chem*, 274, 37965-73. [🔗](#)
- Gazdoui M, Sakurai T, Felsenfeld DP, Cassella MR & Whittard JD (2006). MAP kinase pathway-dependent phosphorylation of the L1-CAM ankyrin binding site regulates neuronal growth. *Mol Biol Cell*, 17, 2696-706. [🔗](#)
- Schmid RS, Midkiff BR, Maness PF & Kedar VP (2004). Adhesion molecule L1 stimulates neuronal migration through Vav2-Pak1 signaling. *Neuroreport*, 15, 2791-4. [🔗](#)
- Schachner M & Maness PF (2007). Neural recognition molecules of the immunoglobulin superfamily: signaling transducers of axon guidance and neuronal migration. *Nat Neurosci*, 10, 19-26. [🔗](#)

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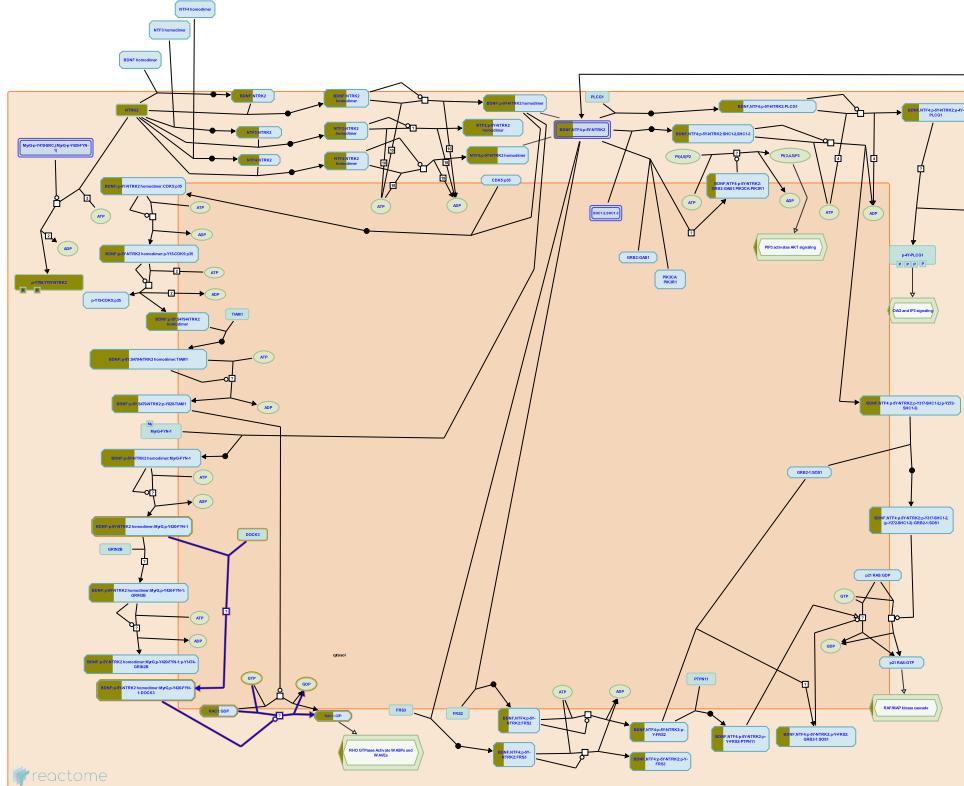
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2008-07-30	Authored	Garapati P V
2009-10-28	Created	Garapati P V

Date	Action	Author
2010-02-16	Reviewed	Maness PF
2021-09-10	Modified	Weiser JD

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1460	P67870	5058	Q13153	5879	P63000

5. NTRK2 activates RAC1 (R-HSA-9032759)



DOCK3-mediated activation of RAC1 downstream of BDNF-induced signaling by NTRK2 (TRKB) plays a role in axonal growth and regeneration. DOCK3 can be recruited to the plasma membrane to activate RAC1 by binding to NTRK-associated FYN (Namekata et al. 2010). Alternatively, DOCK3 can, upon poorly elucidated RHOG activation by the BDNF:NTRK2 complex, bind to the RHOG:GTP complex and activate RAC1 in an ELMO1-dependent manner (Namekata et al. 2012).

References

- Harada T, Namekata K, Guo X, Harada C, Parada LF, Kimura H & Taya C (2010). Dock3 induces axonal outgrowth by stimulating membrane recruitment of the WAVE complex. Proc. Natl. Acad. Sci. U.S.A., 107, 7586-91. 

Harada T, Watanabe H, Namekata K, Kimura A, Guo X, Harada C, ... Kittaka D (2012). Dock3 regulates BDNF-TrkB signaling for neurite outgrowth by forming a ternary complex with Elmo and RhoG. Genes Cells, 17, 688-97. 

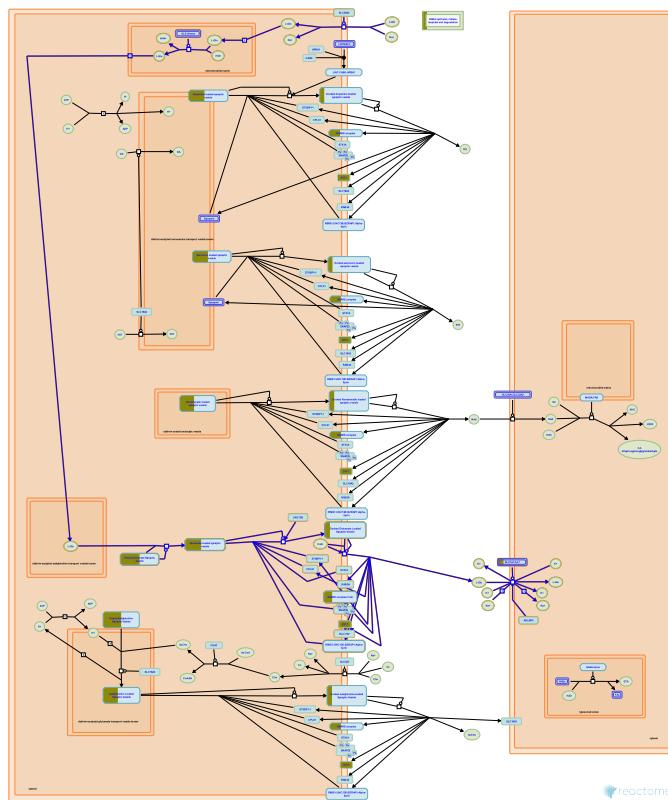
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Date	Action	Author
2017-12-18	Created	Orlic-Milacic M
2018-01-05	Authored	Orlic-Milacic M
2018-02-13	Reviewed	Antila H, Castrén E
2018-02-20	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
4915	Q16620	5879	P63000

6. Glutamate Neurotransmitter Release Cycle (R-HSA-210500)



Communication at the synapse involves the release of glutamate from the presynaptic neuron and its binding to glutamate receptors on the postsynaptic cell to generate a series of events that lead to propagation of the synaptic transmission. This process begins with the formation of synaptic vesicles in the presynaptic neuron, proceeds to the loading of glutamate into the vesicles, and concludes with the release of glutamate into the synaptic cleft.

The glutamate life cycle in the neuron begins with the loading of the nascent synaptic vesicles with cytosolic glutamate with the help the transporter protein, VGLUT1, located in the synaptic vesicular membrane. Glutamate loaded vesicles are formed in the cytoplasm and then transported to a site close to the plasma membrane where the vesicle is docked with the help of several proteins. One of the key players in the docking process is Munc 18, which interacts with syntaxin (in the plasma membrane), MINT (Munc18 interacting molecule), and DOC2. These interactions along with the secondary interactions are needed for docking the synaptic vesicle to the plasma membrane.

The docked synaptic vesicle is not ready for release until it undergoes molecular changes to prime it for fusion with the plasma membrane. Munc13 is one of the main players in the priming process. Munc 13 interacts with RIM (Rab3A interacting molecule) located in the synaptic vesicle. Munc 13 also interacts with DOC2. The precise molecular mechanisms of the interactions that result in docking versus priming are not clear and the docking and priming process have been combined in this annotation of this pathway. Once primed the synaptic vesicle is ready for release.

Synaptic transmission involves an action potential that is generated in the presynaptic cell which induces the opening of voltage gated Ca²⁺ channels (VGCC) located in the plasma membrane of the presynaptic neuron. Typically N, P/Q and R type of VGCCs are involved in the neurotransmitter release. Ca²⁺ influx through these channels results in the rise of intracellular Ca²⁺ concentration. In the microdomain of glutamatergic synapses, the Ca²⁺ concentration could rise between 10-25 micro molar. Synaptotagmin, a Ca²⁺-binding protein located in the synaptic vesicular membrane, responds to the rise in the Ca²⁺ levels in the microdomain and induces a synaptic vesicle membrane curvature that favors vesicle fusion. Fusion of the synaptic vesicle with the plasma membrane is characterized by the formation of a trimeric trans-SNARE complex that involves VAMP2 from the synaptic vesicle membrane, and syntaxin and SNAP-25 from plasma membrane. Vesicle fusion incorporates the synaptic vesicle membrane into the plasma membrane, releasing the vesicle contents (glutamate) into the synaptic cleft. Postfusion the synaptic vesicle membrane proteins (VAMP2, Rab3A, VGLUT1, and synaptotagmin) are also found in the plasma membrane.

References

- Olkkinen VM, Galli T, Riento K, Ehnholm C, Lehtonen E & Jansson S (1998). Interaction of Munc-18-2 with syntaxin 3 controls the association of apical SNAREs in epithelial cells. *J Cell Sci*, 111, 2681-8. [\[Pubmed\]](#)
- Harpold MM, Lory P, Williams ME, Taviaux S, Diriong S & Ellis SB (1995). Chromosomal localization of the human genes for alpha 1A, alpha 1B, and alpha 1E voltage-dependent Ca²⁺ channel subunits. *Genomics*, 30, 605-9. [\[Pubmed\]](#)
- Jahn R, Rosenmund C, Takamori S & Rhee JS (2000). Identification of a vesicular glutamate transporter that defines a glutamatergic phenotype in neurons. *Nature*, 407, 189-94. [\[Pubmed\]](#)
- Südhof TC, Augustin I, Rosenmund C & Brose N (1999). Munc13-1 is essential for fusion competence of glutamatergic synaptic vesicles. *Nature*, 400, 457-61. [\[Pubmed\]](#)
- Andrews-Zwilling YS, Varoqueaux F, Reim K, Kawabe H & Brose N (2006). Binding to Rab3A-interacting molecule RIM regulates the presynaptic recruitment of Munc13-1 and ubMunc13-2. *J Biol Chem*, 281, 19720-31. [\[Pubmed\]](#)

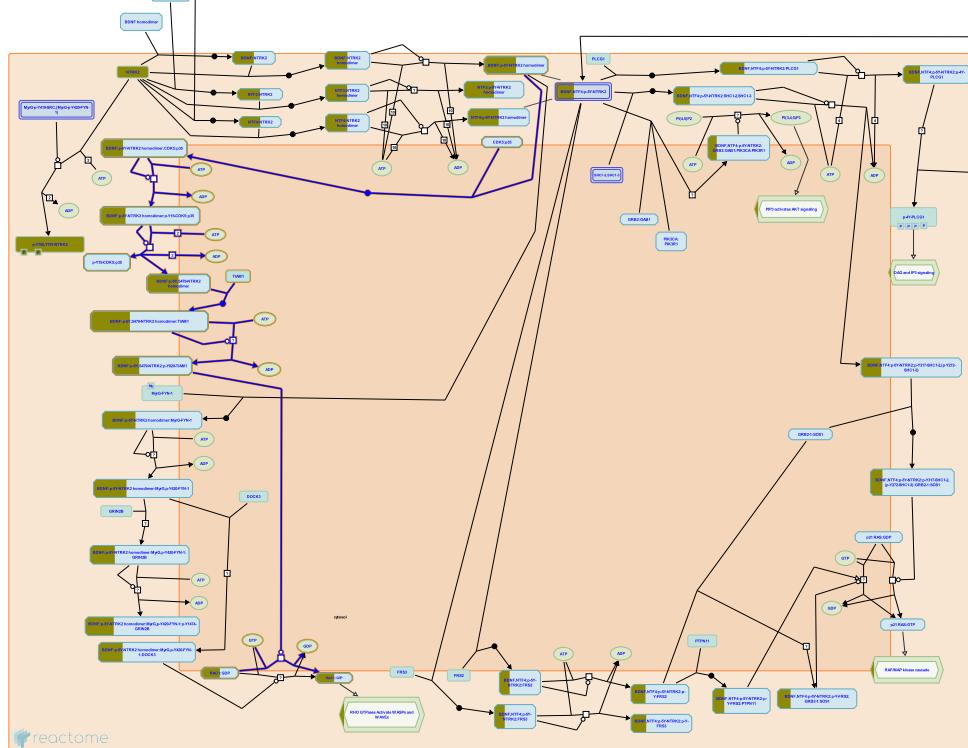
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2008-01-14	Authored	Mahajan SS
2008-01-14	Created	Mahajan SS
2008-04-24	Reviewed	Kavalali E
2021-09-10	Modified	Weiser JD

3 submitted entities found in this pathway, mapping to 3 Reactome entities

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6506	P43004	6844	P63027	6857	P21579

7. Activated NTRK2 signals through CDK5 (R-HSA-9032845)



CDK5, in complex with its activator CDK5R1 (p35), binds to BDNF-activated NTRK2 (TrkB). NTRK2 promotes CDK5 catalytic activity by phosphorylating CDK5 at tyrosine residue Y15 (Cheung et al. 2007), although CDK5 can also be phosphorylated at Y15 independently of NTRK2 (Zhao et al. 2009). CDK5 phosphorylates serine residue S479 of NTRK2 (corresponds to S478 in mouse and rat) (Cheung et al. 2007, Zhao et al. 2009). Phosphorylation of NTRK2 at S479 is needed for BDNF-triggered dendritic growth (Cheung et al. 2007), hippocampal long-term potentiation (LTP) and spatial memory (Lai et al. 2012). These processes involve NTRK2-mediated activation of RHO GTPases RAC1 (Lai et al. 2012) and possibly CDC42 (Cheung et al. 2007). In cultured isolated neurons, phosphorylation at S479 affects localization of NTRK2 (Zhao et al. 2009), but this does not appear to be the case *in vivo* (Lai et al. 2012).

CDK5-mediated phosphorylation of NTRK2 was suggested to influence the level of AKT activity, downstream mTOR signaling and DLG4 (PSD-95) expression, but further elucidation is needed (Lai et al. 2012).

Signaling by TrkB and CDK5 plays a role in inflammation induced hypersensitivity to heat-triggered pain in rats (Zhang et al. 2014).

References

- Palko ME, Xu P, Ip NY, Cheung MC, Lok KC, Cheung ZH, ... Wong AS (2012). TrkB phosphorylation by Cdk5 is required for activity-dependent structural plasticity and spatial memory. *Nat. Neurosci.*, 15, 1506-15. [🔗](#)
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Zhang XQ, Zhang S, Xue QS, Lu H, Shao HJ, Wang WY, ... Yu BW (2014). The BDNF/TrkB signaling pathway is involved in heat hyperalgesia mediated by Cdk5 in rats. PLoS ONE, 9, e85536. [🔗](#)

Huang SH, Li XZ, Sheng AL, Zhang Y, Zhao L, Chen ZY, ... Yin YX (2009). Mechanism underlying activity-dependent insertion of TrkB into the neuronal surface. J. Cell. Sci., 122, 3123-36. [🔗](#)

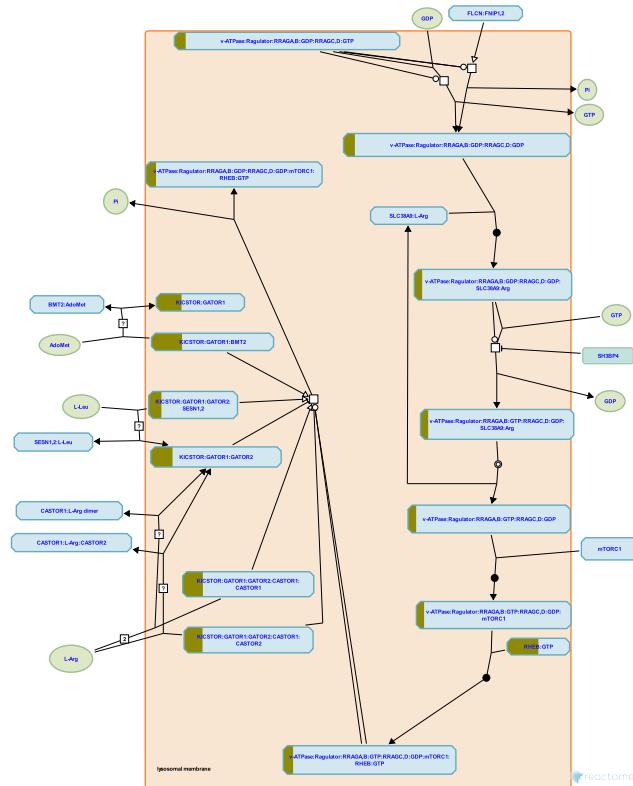
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2018-02-13	Reviewed	Antila H, Castrén E
2018-02-20	Modified	Orlic-Milacic M
2018-02-20	Edited	Orlic-Milacic M

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

Input	UniProt Id	Input	UniProt Id
4915	Q16620	5879	P63000

8. Amino acids regulate mTORC1 (R-HSA-9639288)



The mTORC1 complex acts as an integrator that regulates translation, lipid synthesis, autophagy, and cell growth in response to multiple inputs, notably glucose, oxygen, amino acids, and growth factors such as insulin (reviewed in Sabatini 2017, Meng et al. 2018, Kim and Guan 2019).

MTOR, the kinase subunit of mTORC1, is activated by interaction with RHEB:GTP at the cytosolic face of lysosomal membrane (Long et al. 2005, Tee et al. 2005, Long et al. 2007, Yang et al. 2017). Recruitment of mTORC1 to the lysosomal membrane is intricate and incompletely understood. At the center of the system is a complex of two small GTPases, the Rag heterodimer (RRAGA or RRAGB bound to RRAGC or RRAGD). The Rag heterodimer is tethered to the membrane by the Ragulator complex, which also binds the v-ATPase complex. The Rag heterodimer acts as a cross-regulating switch, with the binding of GTP by one subunit inhibiting the exchange of GDP for GTP by the other subunit (Shen et al. 2017). The active conformation of the Rag heterodimer that recruits mTORC1 to the lysosomal membrane is RRAGA,B:GTP:RRAGC,D:GDP while the inactive conformation, RRAGA,B:GDP:RRAGC,D:GTP, releases mTORC1 (Sancak et al. 2008, Kim et al. 2008, Sancak et al. 2010, Lawrence et al. 2018). GTPase activating proteins (GAPs) and guanyl nucleotide exchange factors (GEFs) acting upon the Rag heterodimer thereby regulate recruitment of mTORC1. RHEB:GTP at the lysosomal membrane also binds mTORC1 and directly activates mTORC1. During inactivation of mTORC1 in response to removal of amino acids, the TSC complex, a GAP for RHEB, is required in addition to the inactive Rag complex to release mTORC1 from RHEB and hence fully release mTORC1 from the lysosomal membrane (Demetriades et al. 2014).

Amino acids regulate recruitment of mTORC1 to the lysosomal membrane by at least 4 mechanisms (reviewed in Zhuang et al. 2019, Wolfson and Sabatini 2017, Yao et al. 2017). 1) Sestrin1 (SESN1) or Sestrin2 (SESN2) binds leucine and the Sestrin1,2:leucine complex is then released from the GATOR2 complex, allowing GATOR2 to positively regulate mTORC1 activation (Chantranupong et al. 2014, Parmigiani et al. 2014, Kim et al. 2015, Wolfson et al. 2016, Saxton et al. 2016). 2) CASTOR1 in a homodimer or a heterodimer with CASTOR2 binds arginine and the CASTOR1:arginine complex is likewise released from GATOR2, allowing GATOR2 to activate mTORC1 (Chantranupong et al. 2016, Saxton et al. 2016, Gai et al. 2016, Xia et al. 2016). 3) BMT2 (SAMTOR), a negative regulator of mTORC1 activation, binds S-adenosylmethionine (SAM), a derivative of methionine (Gu et al. 2017). The binding of SAM causes BMT2 to dissociate from GATOR1, allowing the activation of mTORC1. 4) The amino acid transporter SLC38A9 binds arginine and SLC38A9 then acts as a GEF to convert RRAGA,B:GDP to the active form, RRAGA,B:GTP (Rebsamen et al. 2015, Wang et al. 2015, Wyant et al. 2017, Shen and Sabatini 2018). Amino acid starvation also regulates the assembly of the V0 and V1 subunits of v-ATPase by an uncharacterized mechanism (Stransky and Forgac 2015) and v-ATPase is required for activation of mTORC1 by amino acids (Zoncu et al. 2011). Glutamine activates mTORC1 by a mechanism that is independent of the Rag GTPases, requires ARF1, but is not yet fully elucidated (Jewell et al. 2015).

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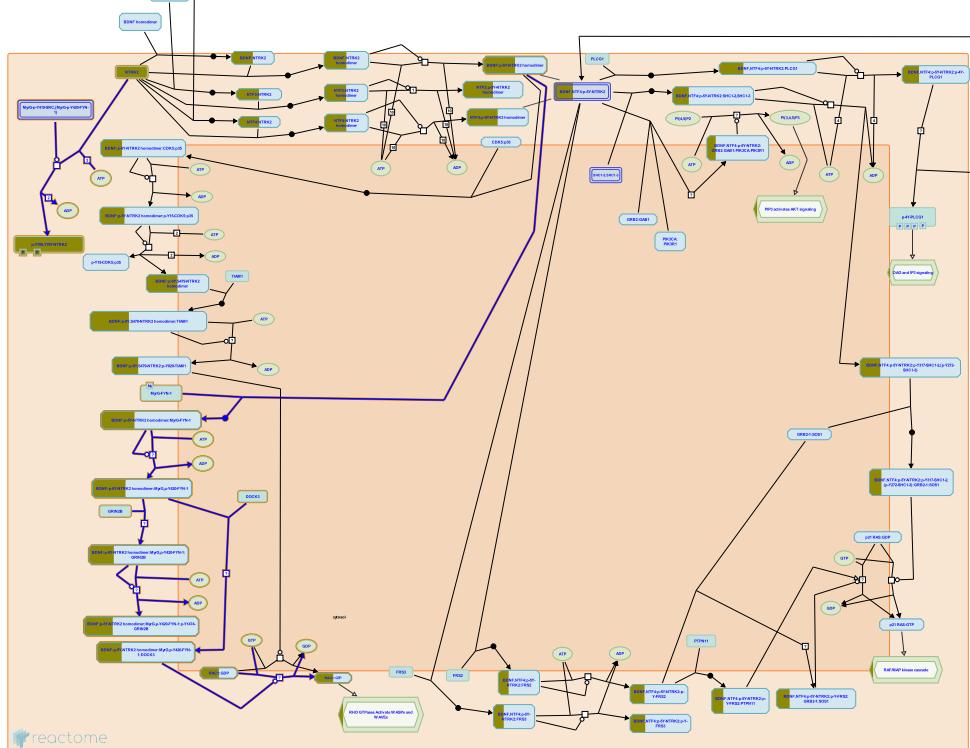
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2019-03-04	Authored	May B
2019-03-09	Created	May B
2019-08-08	Reviewed	Condon KJ, Sabatini DM
2021-09-10	Modified	Weiser JD

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

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11133	Q9Y664	6009	Q15382

Input	UniProt Id	Input	UniProt Id
816	P36543	9681	O75140

9. Activated NTRK2 signals through FYN (R-HSA-9032500)



In mouse brain, Fyn activation downstream of Bdnf-induced Ntrk2 (TrkB) signaling results in increased protein levels of AMPA receptor subunits Gria2 (GluR2), Gria3 (GluR3) and Gria1 (GluR1) without change in mRNA levels (Narisawa-Saito et al. 1999).

BDNF-mediated activation of NTRK2 increases phosphorylation of voltage gated sodium channels by FYN, resulting in decrease of sodium currents (Ahn et al. 2007).

FYN activation downstream of NTRK2 is implicated in oligodendrocyte myelination and contributes to BDNF-induced activation of ERK1/2 (MAPK3/1) through an unknown mechanism (Peckham et al. 2015).

Besides acting downstream of NTRK2, FYN and other SRC kinases, activated by other receptors such as GPCRs, may phosphorylate NTRK2 and enhance its catalytic activity (Rajagopal and Chao 2006, Huang and McNamara 2010).

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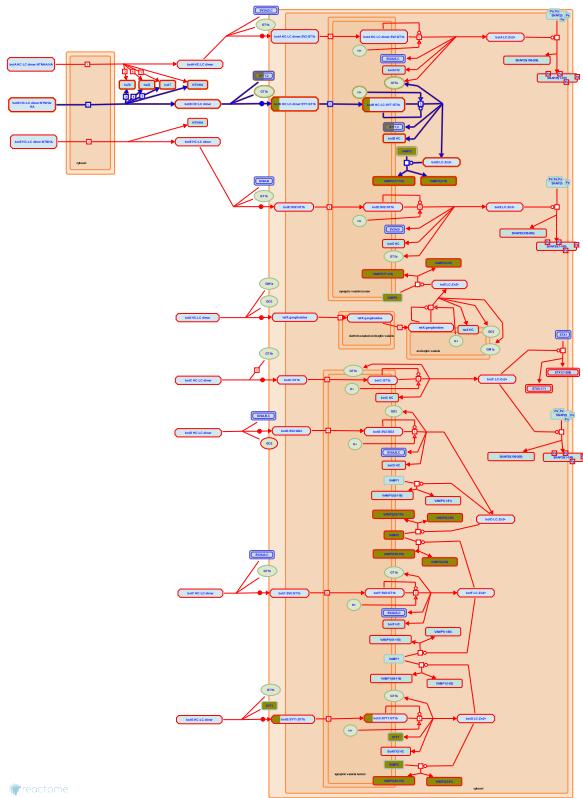
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2018-01-05	Authored	Orlic-Milacic M
2018-02-13	Reviewed	Antila H, Castrén E
2018-02-20	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
4915	Q16620	5879	P63000

10. Toxicity of botulinum toxin type B (botB) (R-HSA-5250958)



Diseases: botulism.

Botulinum toxin type B (botB, also known as BoNT/B), a disulfide-bonded heavy chain (HC) - light chain (LC) heterodimer, enters the gut typically as a result of consuming contaminated food (Hatheway 1995), as a complex with nontoxic nonhemagglutinin protein (NTNHA, encoded by the *C. botulinum* *ntnha* gene) and multiple copies of three hemagglutinin proteins (HA, encoded by the *C. botulinum* *ha17*, *ha34*, and *ha70* genes) (Amatsu et al. 2013). The complex protects the toxin from degradation in the gut and mediates its association with the gut epithelium and transcytosis to enter the circulation (Fujinaga et al. 2013). Circulating toxin molecules associate with gangliosides and synaptotagmin (SYT) proteins exposed by exocytosis at a synapse of a target neuron (Dong et al. 2003; Yowler & Schengrund 2004). Vesicle recycling brings the toxin into the neuron where the vesicle is acidified (Sudhoff 2004). The lowered pH induces a conformational change in the toxin: its HC forms a passage in the vesicle membrane through which its LC is extruded into the neuronal cytosol. The HC - LC disulfide bond is reduced (Montal 2010). The LC then catalyzes the cleavage of vesicle-associated membrane protein 2 (VAMP2) on the cytosolic face of synaptic vesicle membranes (Foran et al. 1994; Schiavo et al. 1992), thereby inhibiting synaptic vesicle fusion with the plasma membrane and exocytosis.

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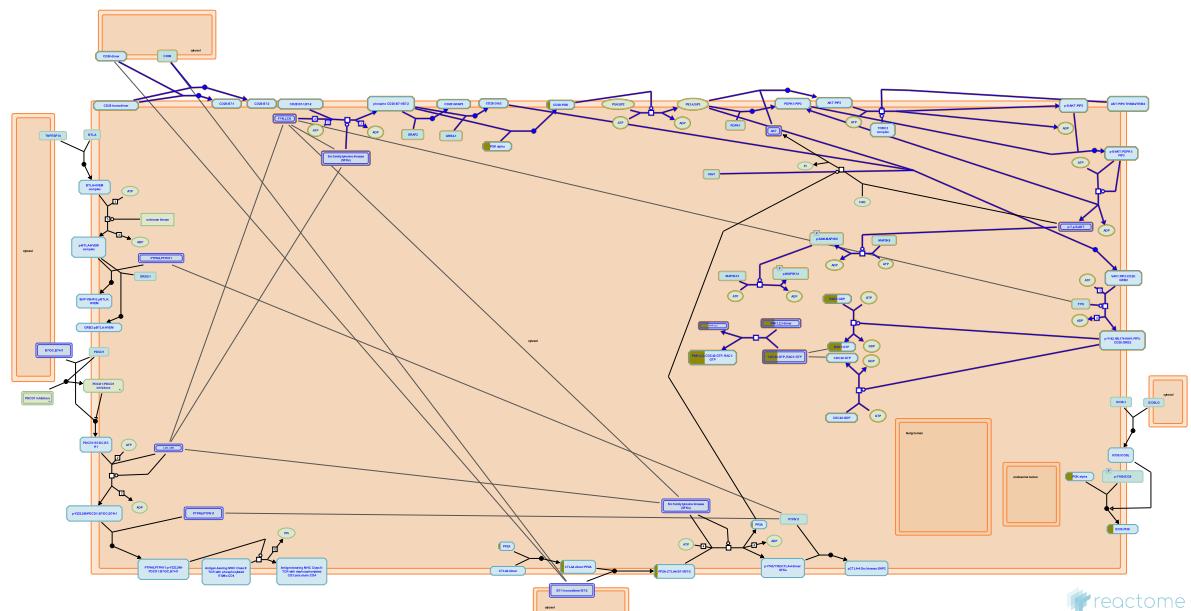
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2007-08-03	Reviewed	Ichtchenko K
2014-02-01	Created	D'Eustachio P
2014-02-11	Revised	D'Eustachio P
2014-02-11	Edited	D'Eustachio P
2014-11-18	Reviewed	Sharma S, Thirunavukkarasu N
2020-10-08	Modified	D'Eustachio P

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

Input	UniProt Id	Input	UniProt Id
6844	P63027	6857	P21579

11. CD28 co-stimulation (R-HSA-389356)



reactome

In naive T cells, CD28 costimulation enhances cell cycle entry, potently stimulates expression of both the mitogenic lymphokine interleukin-2 (IL-2) and its receptor, and stimulates the activation of an antiapoptotic program. CD28 engages with one or both members of the B7 receptor family, B7.1 and B7.2. Upon ligand binding the tyrosines and proline-rich motifs present in the cytoplasmic tail of CD28 are phosphorylated by Lck or Fyn. Upon phosphorylation CD28 recruits and induces phosphorylation and activation of a more restricted set of intracellular signaling components that, together with those mobilized by the TCR, contribute to convert membrane-based biochemical and biophysical changes into gene activation events. Proteins like PI3K, Vav-1, Tec and Itk kinases, AKT, and the Dok-1 adaptor have been identified as elements of the CD28 signaling pathway by biochemical or genetic approaches or both.

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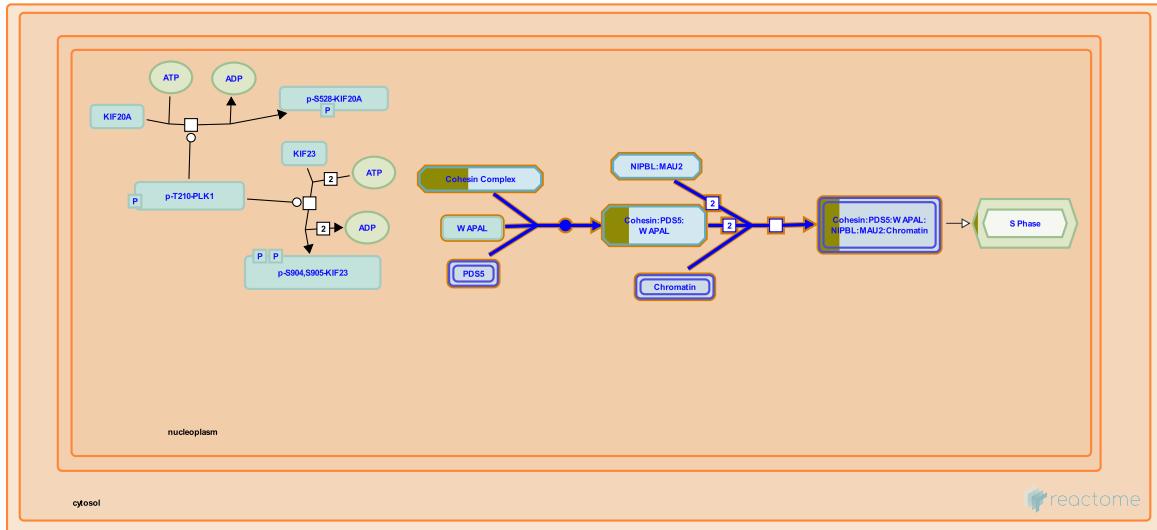
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2008-12-16	Authored	Garapati P V
2009-01-06	Created	Garapati P V
2009-06-01	Reviewed	Bluestone JA, Esensten J
2021-09-20	Modified	Weiser JD

3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
5058	Q13153	5296	O00459	5879	P63000

12. Cohesin Loading onto Chromatin (R-HSA-2470946)



Cellular compartments: nucleoplasm.

In mitotic telophase, as chromosomes decondense, cohesin complex associated with PDS5 (PDS5A and PDS5B) and WAPAL (WAPL) proteins is loaded onto chromatin (Shintomi and Hirano, 2009, Kueng et al. 2006, Gandhi et al. 2006, Chan et al. 2012). Cohesin loading is facilitated by the complex of NIPBL (SCC2) and MAU2 (SCC4) proteins, which constitute an evolutionarily conserved cohesin loading complex. MAU2 depletion in HeLa cells results in 2-3-fold reduction in the amount of cohesin in the chromatin fraction (Watrin et al. 2006). NIPBL mutations are the cause of the Cornelia de Lange syndrome, a dominantly inherited disorder characterized by facial malformations, limb defects, and growth and cognitive retardation (Tonkin et al. 2004). Cornelia de Lange syndrome can also be caused by mutations in cohesin subunits SMC1A (Musio et al. 2006, Borck et al. 2007, Deardorff et al. 2007, Pie et al. 2010) and SMC3 (Deardorff et al. 2007).

References

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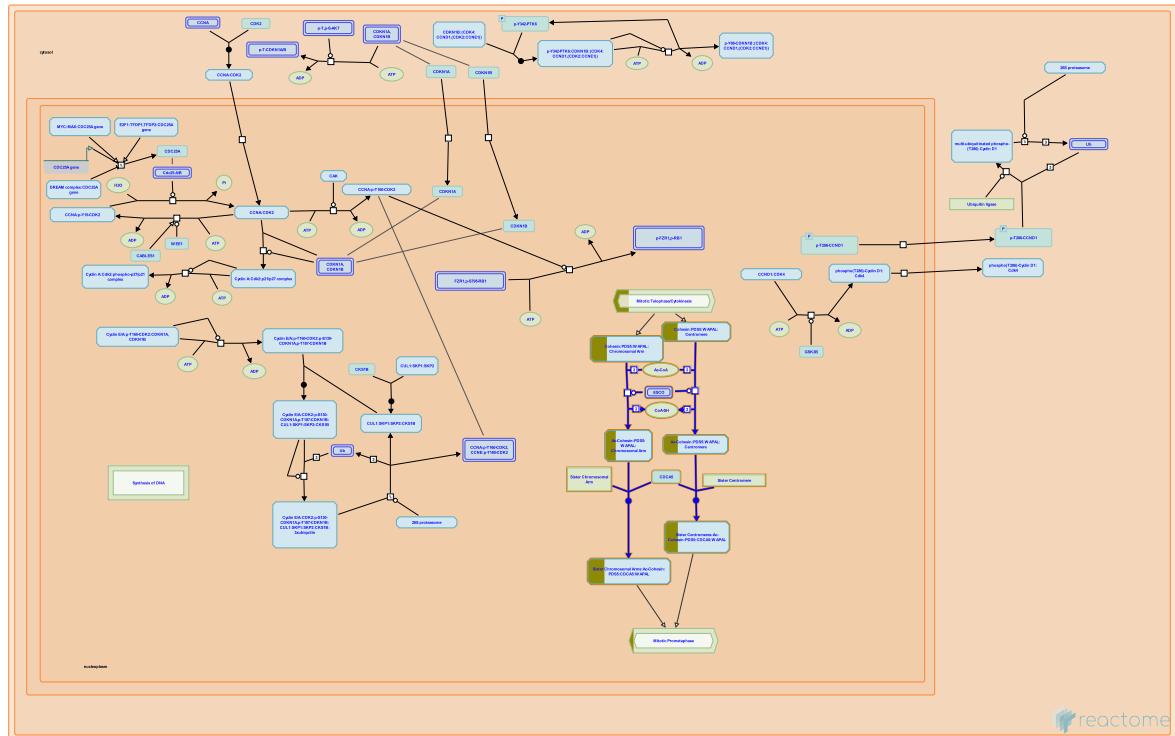
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2012-10-05	Edited	Matthews L, Gillespie ME
2012-10-22	Reviewed	Zhang N
2012-11-20	Reviewed	Tanno Y, Watanabe Y
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
5885	O60216	8243	Q14683

13. Establishment of Sister Chromatid Cohesion (R-HSA-2468052)



Cellular compartments: nucleoplasm, chromosome, centromeric region, chromosome.

The cohesin complex loads onto chromatin in telophase, but its association with chromatin remains transient, dynamic until the S-phase of the cell cycle, presumably because the cohesin-bound NIPBL:MAU2 (SCC2:SCC4) complex promotes chromatin loading, while cohesin-bound WAPAL promotes dissociation from chromatin. Stable binding of cohesin complexes to chromatin, measured by a mean residence time on chromatin, is triggered by DNA replication in S-phase (Gerlich et al. 2006), consistent with establishment of sister chromatid cohesion.

In S-phase, acetyltransferases ESCO1 and ESCO2 acetylate the SMC3 cohesin subunit (Hou and Zou 2005, Zhang et al. 2008, Nishiyama et al. 2010, Whelan et al. 2012). The acetylation of SMC3, in addition to DNA replication and the presence of PDS5 on cohesin, facilitates the recruitment of CDCA5 (Sororin) to cohesin complexes, an essential step in the establishment of sister chromatid cohesion in mammalian cells (Rankin et al. 2005, Nishiyama et al. 2010). CDCA5 (Sororin) displaces WAPAL from PDS5, thus preventing WAPAL to interfere with the establishment of sister chromatid cohesion (Nishiyama et al. 2010). The establishment and temporal regulation of sister chromatid cohesion is necessary for equal segregation of replicated chromosomes to daughter cells.

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2012-10-22	Reviewed	Zhang N
2012-11-20	Reviewed	Tanno Y, Watanabe Y
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
5885	O60216	8243	Q14683

14. Killing mechanisms ([R-HSA-9664420](#))

WNT5:FZD7-mediated leishmania damping



Diseases: cutaneous leishmaniasis.

The long-lasting Leishmania infection is established within macrophages in which the most effective killing response is the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). (Rossi and Fasel 2018). Additionally, autophagy has been described as an innate immune mechanism for eliminating intracellular pathogens, although its role in restricting Leishmania replication is unclear (Veras et al. 2019)

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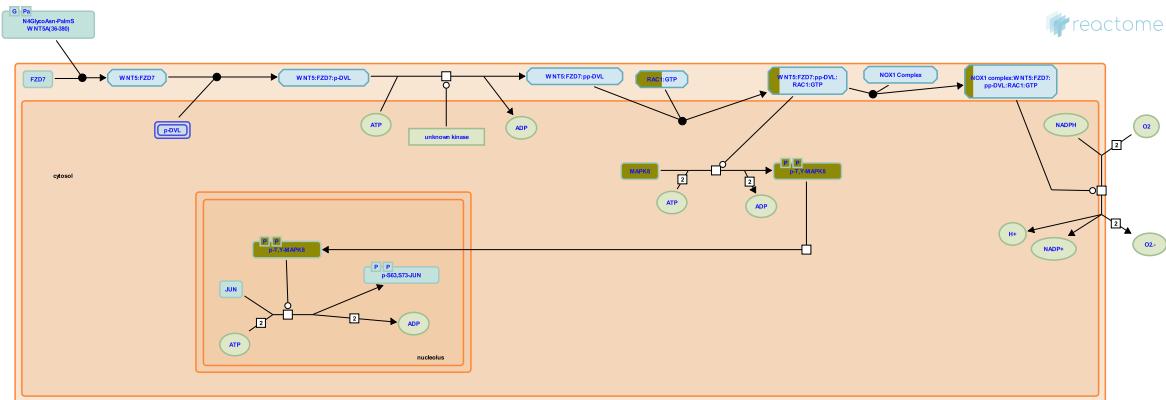
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2020-01-07	Authored	Jassal B
2020-01-29	Authored	Murillo JI
2020-02-04	Reviewed	Gregory DJ
2020-02-05	Edited	Jassal B, Murillo JI
2020-02-06	Modified	Murillo JI

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

Input	UniProt Id	Input	UniProt Id
1496	P45983	5879	P63000

15. WNT5:FZD7-mediated leishmania damping (R-HSA-9673324)



Diseases: cutaneous leishmaniasis.

Wnt-5a (WNT5) is known for being a highly specific regulated gene in response to microbial infection (Blumenthal et al. 2006, Pereira et al. 2008 & Ljungberg et al. 2019) including leishmaniasis (Chakraborty et al. 2017), where it seems to be involved in mechanisms that dampen the parasite load within main host macrophages (Chakraborty et al. 2017). In addition, WNT5 is a highly responsive gene in human macrophages present in chronic diseases such as rheumatoid arthritis (Sen et al. 2000), cancer (Pukrop et al. 2006), atherosclerosis (Christman et al. 2008) and obesity (Ouchi et al. 2010 & Ljungberg et al. 2019).

Frizzled-7 (FZD7) acts as a receptor of WNT5 which, upon binding, is implicated in the initiation of the non-canonical WNT pathway that ends up in the re-accommodation of the cytoskeleton to allow a process called planar cell polarity (PCP) (Ljungberg et al. 2019). The activation of the WNT5:FZD7 non-canonical signalling cascade that drives PCP is being studied for its involvement in inflammatory responses (Shao et al. 2016). Treatment of RAW264.7 macrophages with recombinant Wnt5a induced NADPH oxidase-mediated ROS production, which has been suggested to contribute to the macrophage control of *L. donovani*. Consequently, detailed understanding of how WNT signaling network defines host responses to infection could be important to identify potential targets (Ljungberg et al. 2019).

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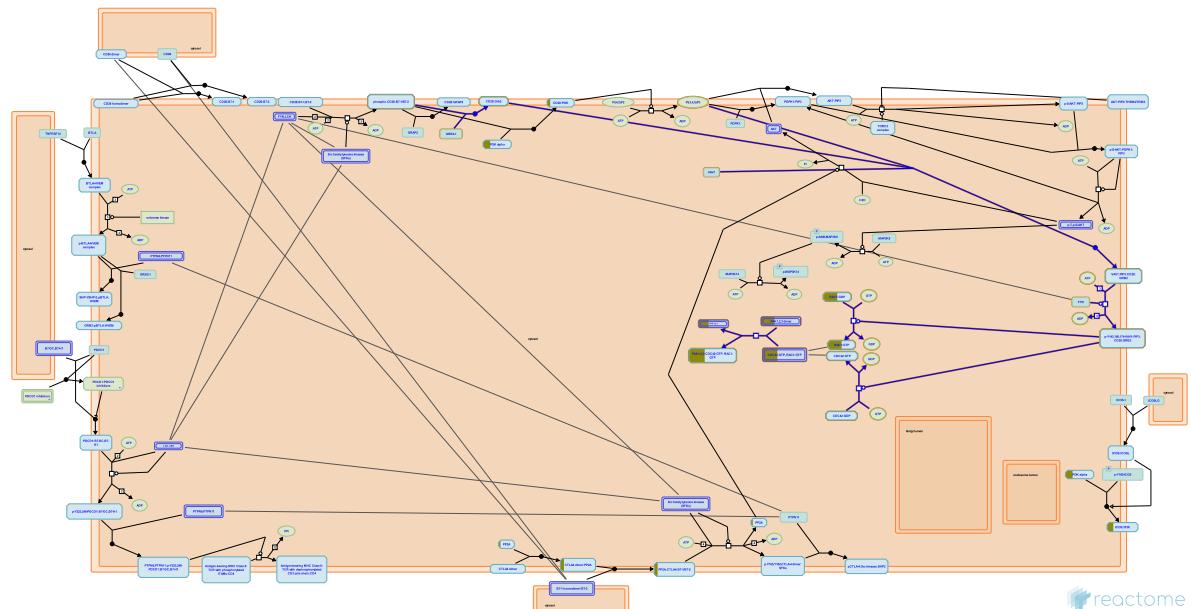
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2020-01-09	Authored	Jassal B, Murillo JI
2020-02-04	Reviewed	Gregory DJ
2020-02-06	Modified	Murillo JI

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

Input	UniProt Id	Input	UniProt Id
1496	P45983	5879	P63000

16. CD28 dependent Vav1 pathway (R-HSA-389359)



CD28 binds to several intracellular proteins including PI3 kinase, Grb-2, Gads and ITK. Grb-2 specifically co-operates with Vav-1 in the up-regulation of NFAT/AP-1 transcription. CD28 costimulation resulted in a prolonged and sustained phosphorylation and membrane localization of Vav1 in comparison to T-cell receptor activation alone. Tyrosine-phosphorylated Vav1 is an early point of integration between the signaling routes triggered by the T-cell receptor and CD28.

Vav1 transduces TCR and co-stimulatory signals to multiple biochemical pathways and several cytoskeleton-dependent processes. The products of Vav1 activation, Rac1 and Cdc42, in turn activate the mitogen-activated protein kinases JNK and p38. Vav1 is also required for TCR-induced calcium flux, activation of the ERK MAP kinase pathway, activation of the NF- κ B transcription factor, inside-out activation of the integrin LFA-1, TCR clustering, and polarisation of the T cell.

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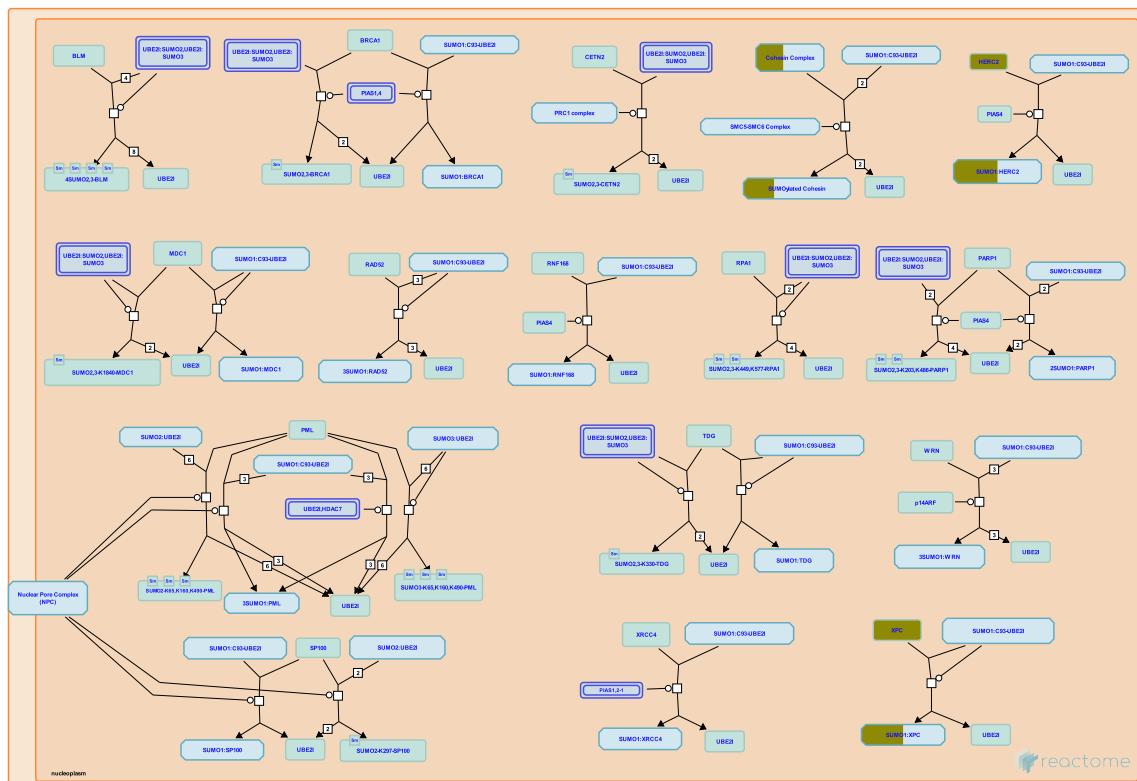
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2009-01-06	Created	Garapati P V
2009-06-01	Reviewed	Bluestone JA, Esensten J
2021-09-20	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
5058	Q13153	5879	P63000

17. SUMOylation of DNA damage response and repair proteins (R-HSA-3108214)



Cellular compartments: nucleoplasm.

Several factors that participate in DNA damage response and repair are SUMOylated (reviewed in Dou et al. 2011, Bekker-Jensen and Mailand 2011, Ulrich 2012, Psakhye and Jentsch 2012, Bologna and Ferrari 2013, Flotho and Melchior 2013, Jackson and Durocher 2013). SUMOylation can alter enzymatic activity and protein stability or it can serve to recruit additional factors. For example, SUMOylation of Thymine DNA glycosylase (TDG) causes TDG to lose affinity for its product, an abasic site opposite a G residue, and thus increases turnover of the enzyme. During repair of double-strand breaks SUMO1, SUMO2, SUMO3, and the SUMO E3 ligases PIAS1 and PIAS4 accumulate at double-strand breaks where BRCA1, HERC1, RNF168, MDC1, and TP53BP1 are SUMOylated. SUMOylation of BRCA1 may increase its ubiquitin ligase activity while SUMOylation of MDC1 and HERC2 appears to play a role in recruitment of proteins such as RNF4 and RNF8 to double strand breaks. Similarly SUMOylation of RPA1 (RPA70) recruits RAD51 in the homologous recombination pathway.

References

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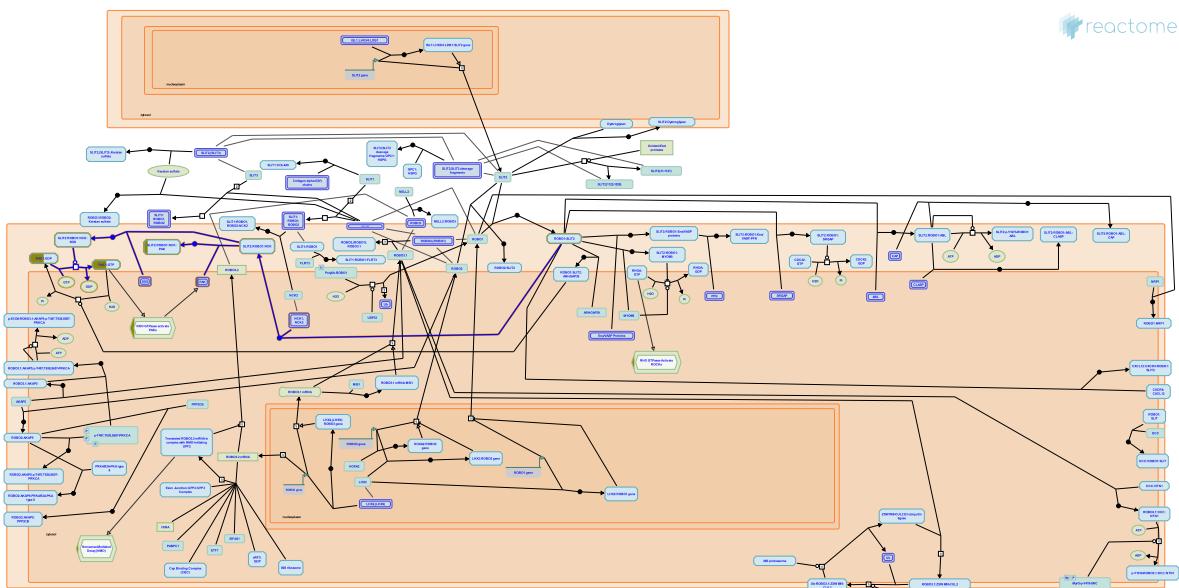
Edit history

Date	Action	Author
2013-02-06	Edited	May B
2013-02-06	Authored	May B
2013-02-10	Created	May B
2015-02-21	Reviewed	Ferrari S
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
5885	O60216	7508	Q01831
8243	Q14683	8924	O95714

18. Activation of RAC1 (R-HSA-428540)



A low level of RAC1 activity is essential to maintain axon outgrowth. ROBO activation recruits SOS, a dual specificity GEF, to the plasma membrane via Dock homolog NCK (NCK1 or NCK2) to activate RAC1 during midline repulsion.

References

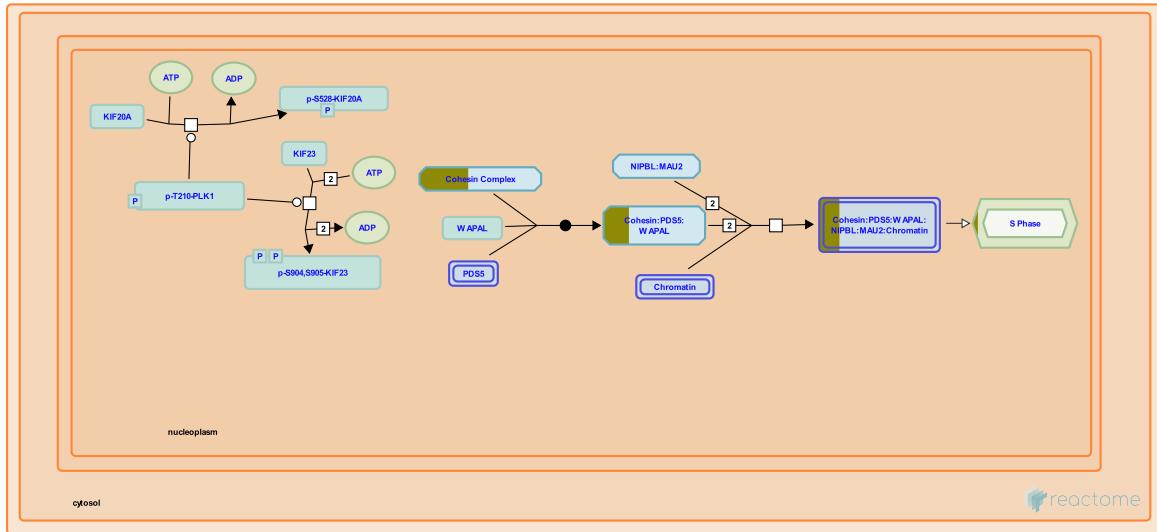
Edit history

Date	Action	Author
2008-09-05	Edited	Garapati P V
2008-09-05	Authored	Garapati P V
2009-07-06	Created	Garapati P V
2009-08-18	Reviewed	Kidd T
2017-06-26	Edited	Orlic-Milacic M
2017-07-31	Reviewed	Jaworski A
2020-11-11	Modified	D'Eustachio P

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

Input	UniProt Id	Input	UniProt Id
5058	Q13153	5879	P63000

19. Mitotic Telophase/Cytokinesis (R-HSA-68884)



In this final phase of mitosis, new membranes are formed around two sets of chromatids and two daughter cells are formed. The chromosomes and the spindle fibers disperse, and the fiber ring around the center of the cell, composed of actin, contracts, pinching the cell into two daughter cells.

References

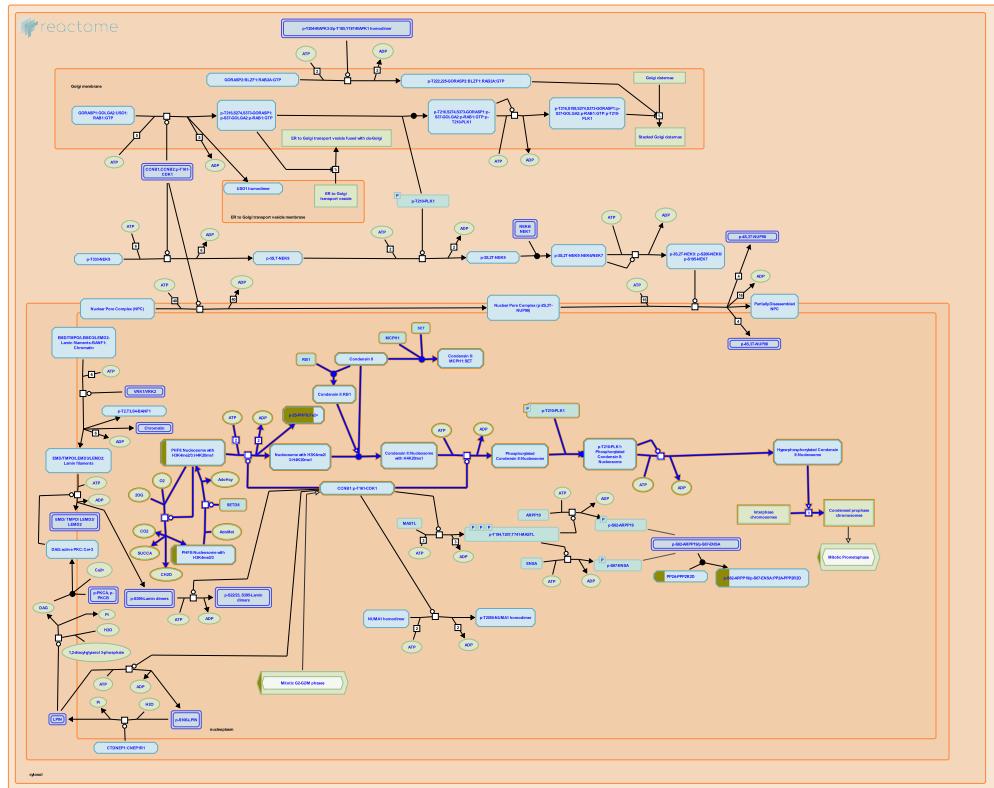
Edit history

Date	Action	Author
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
5885	O60216	8243	Q14683

20. Condensation of Prophase Chromosomes ([R-HSA-2299718](#))



Cellular compartments: nucleoplasm.

In mitotic prophase, the action of the condensin II complex enables initial chromosome condensation.

The condensin II complex subunit NCAPD3 binds monomethylated histone H4 (H4K20me1), thereby associating with chromatin (Liu et al. 2010). Binding of the condensin II complex to chromatin is partially controlled by the presence of RB1 (Longworth et al. 2008).

Two mechanisms contribute to the accumulation of H4K20me1 at mitotic entry. First, the activity of SETD8 histone methyltransferase peaks at G2/M transition (Nishioka et al. 2002, Rice et al. 2002, Wu et al. 2010). Second, the complex of CDK1 and cyclin B1 (CDK1:CCNB1) phosphorylates PHF8 histone demethylase at the start of mitosis, removing it from chromatin (Liu et al. 2010).

Condensin II complex needs to be phosphorylated by the CDK1:CCNB1 complex, and then phosphorylated by PLK1, in order to efficiently condense prophase chromosomes (Abe et al. 2011).

References

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Nagasaki K, Hirota T, Aoyagi Y, Abe S, Kozuka-Hata H, Obuse C, ... Hirayama Y (2011). The initial phase of chromosome condensation requires Cdk1-mediated phosphorylation of the CAP-D3 subunit of condensin II. *Genes Dev.*, 25, 863-74. [🔗](#)

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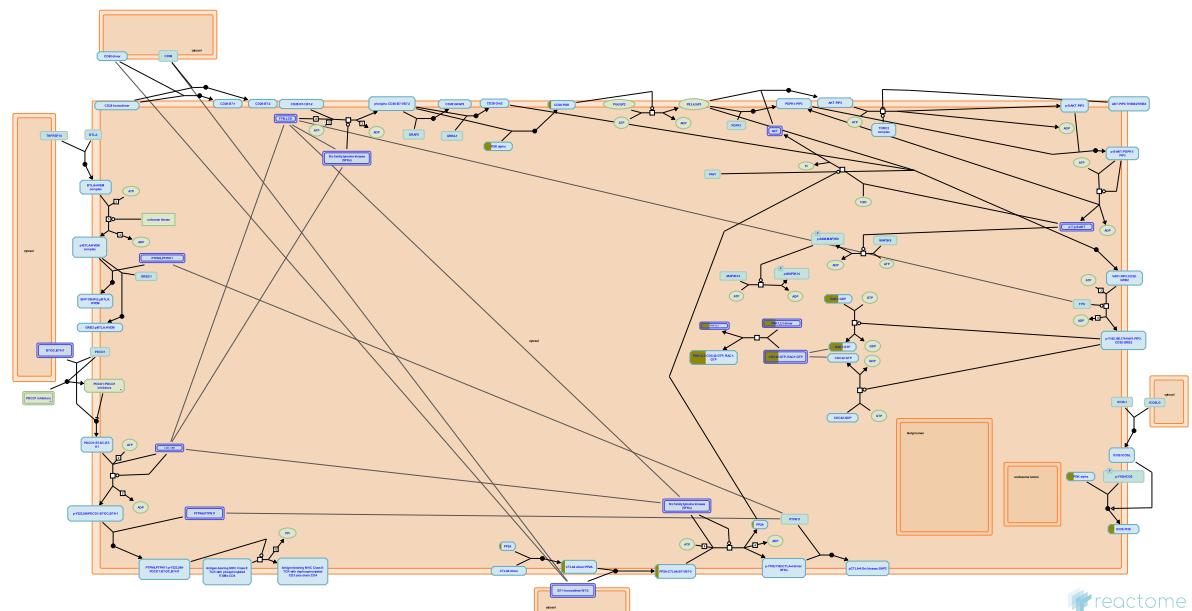
Edit history

Date	Action	Author
2012-06-04	Created	Orlic-Milacic M
2013-04-11	Authored	Gallie BL
2013-04-23	Edited	Matthews L
2013-04-23	Authored	Orlic-Milacic M
2013-10-14	Reviewed	Longworth MS
2021-09-10	Modified	Weiser JD

1 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id
23133	Q9UPP1-1, Q9UPP1-2, Q9UPP1-3

21. Costimulation by the CD28 family (R-HSA-388841)



Cellular compartments: plasma membrane.

Optimal activation of T-lymphocytes requires at least two signals. A primary one is delivered by the T-cell receptor (TCR) complex after antigen recognition and additional costimulatory signals are delivered by the engagement of costimulatory receptors such as CD28. The best-characterized costimulatory pathways are mediated by a set of cosignaling molecules belonging to the CD28 superfamily, including CD28, CTLA4, ICOS, PD1 and BTLA receptors. These proteins deliver both positive and negative second signals to T-cells by interacting with B7 family ligands expressed on antigen presenting cells. Different subsets of T-cells have very different requirements for costimulation. CD28 family mediated costimulation is not required for all T-cell responses *in vivo*, and alternative costimulatory pathways also exist. Different receptors of the CD28 family and their ligands have different regulation of expression. CD28 is constitutively expressed on naive T cells whereas CTLA4 expression is dependent on CD28/B7 engagement and the other receptor members ICOS, PD1 and BTLA are induced after initial T-cell stimulation.

The positive signals induced by CD28 and ICOS molecules are counterbalanced by other members of the CD28 family, including cytotoxic T-lymphocyte associated antigen (CTLA)4, programmed cell death (PD)1, and B and T lymphocyte attenuator (BTLA), which dampen immune responses. The balance of stimulatory and inhibitory signals is crucial to maximize protective immune responses while maintaining immunological tolerance and preventing autoimmunity.

The costimulatory receptors CD28, CTLA4, ICOS and PD1 are composed of single extracellular IgV-like domains, whereas BTLA has one IgC-like domain. Receptors CTLA4, CD28 and ICOS are covalent homodimers, due to an interchain disulphide linkage. The costimulatory ligands B71, B72, B7H2, B7H1 and B7DC, have a membrane proximal IgC-like domain and a membrane distal IgV-like domain that is responsible for receptor binding and dimerization. CD28 and CTLA4 have no known intrinsic enzymatic activity. Instead, engagement by their physiologic ligands B71 and B72 leads to the physical recruitment and activation of downstream T-cell effector molecules.

References

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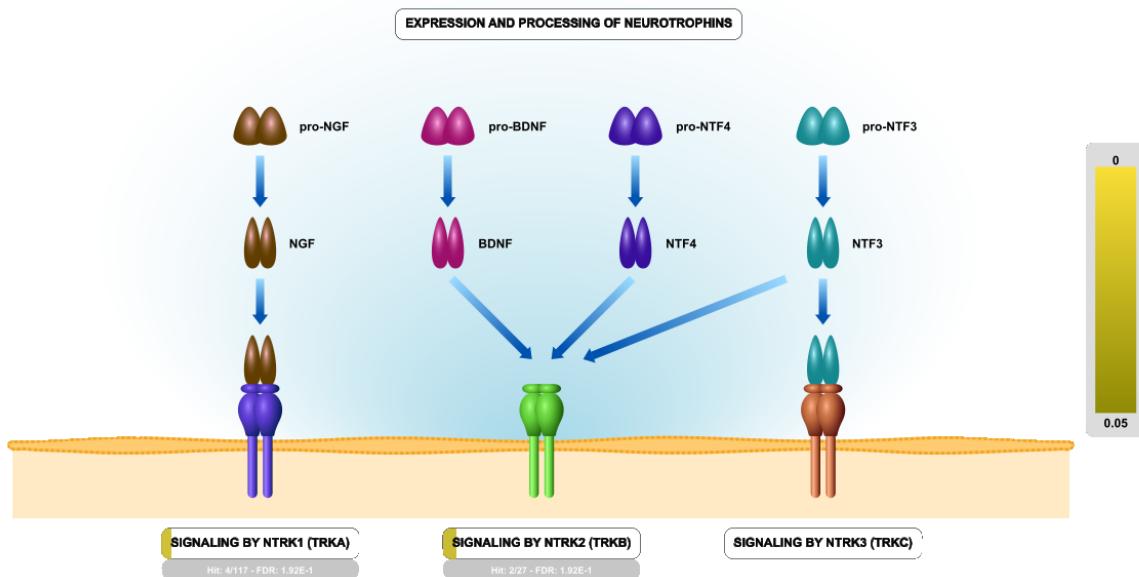
Edit history

Date	Action	Author
2008-12-16	Edited	Garapati P V
2008-12-16	Authored	Garapati P V
2008-12-16	Created	Garapati P V
2009-06-01	Reviewed	Bluestone JA, Esensten J
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
5058	Q13153	5296	O00459
5515	P67775	5879	P63000

22. Signaling by NTRKs (R-HSA-166520)



Neurotrophins (NGF, BDNF, NTF3 and NTF4) play pivotal roles in survival, differentiation, and plasticity of neurons in the peripheral and central nervous system. They are produced, and secreted in minute amounts, by a variety of tissues. They signal through two types of receptors: NTRK (TRK) tyrosine kinase receptors (TRKA, TRKB, TRKC), which differ in their preferred neurotrophin ligand, and p75NTR death receptor, which interacts with all neurotrophins. Besides the nervous system, TRK receptors and p75NTR are expressed in a variety of other tissues. For review, please refer to Bibel and Barde 2000, Poo 2001, Lu et al. 2005, Skaper 2012, Park and Poo 2013.

NTRK receptors, NTRK1 (TRKA), NTRK2 (TRKB) and NTRK3 (TRKC) are receptor tyrosine kinases activated by ligand binding to their extracellular domain. Ligand binding induces receptor dimerization, followed by trans-autophosphorylation of dimerized receptors on conserved tyrosine residues in the cytoplasmic region. Phosphorylated tyrosines in the intracellular domain of the receptor serve as docking sites for adapter proteins, triggering downstream signaling cascades.

NTRK1 (TRKA) is the receptor for the nerve growth factor (NGF). NGF is primarily secreted by tissues that are innervated by sensory and sympathetic neurons. NTRK1 signaling promotes growth and survival of neurons during embryonic development and maintenance of neuronal cell integrity in adulthood (reviewed by Marlin and Li 2015).

Brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NTF4, also known as NT-4) are two high affinity ligands for NTRK2 (TRKB). Neurotrophin-3 (NTF3, also known as NT-3) binds to NTRK2 with low affinity and may not be a physiologically relevant ligand. Nerve growth factor (NGF), a high affinity ligand for NTRK1, does not interact with NTRK2. NTRK2 signaling is implicated in neuronal development in both the peripheral (PNS) and central nervous system (CNS) and may play a role in long-term potentiation (LTP) and learning (reviewed by Minichiello 2009). NTRK2 may modify neuronal excitability and synaptic transmission by directly phosphorylating voltage gated channels (Rogalski et al. 2000).

NTF3 (NT-3) is the ligand for NTRK3 (TRKC). Signaling downstream of activated NTRK3, regulates cell survival, proliferation and motility. In the absence of its ligand, NTRK3 functions as a dependence receptor and triggers BAX and CASP9-dependent cell death (Tauszig-Delamasure et al. 2007, Ichim et al. 2013).

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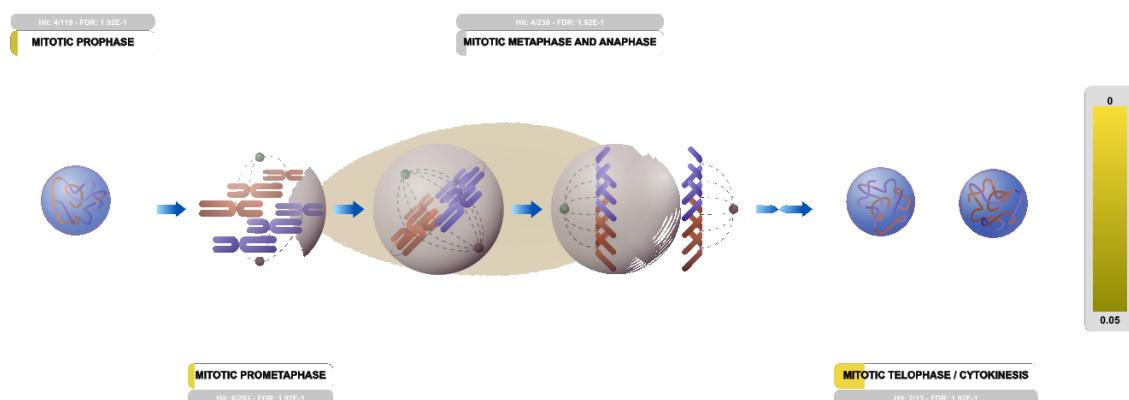
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Date	Action	Author
2005-09-07	Created	Jassal B
2006-10-10	Edited	Jassal B
2006-10-10	Authored	Annibali D, Nasi S
2007-11-08	Reviewed	Greene LA
2021-09-10	Modified	Weiser JD

5 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
4915	Q16620	5296	O00459	5515	P67775
5879	P63000	5898	P11233		

23. M Phase (R-HSA-68886)



Mitosis, or the M phase, involves nuclear division and cytokinesis, where two identical daughter cells are produced. Mitosis involves prophase, prometaphase, metaphase, anaphase, and telophase. Finally, cytokinesis leads to cell division. The phase between two M phases is called the interphase; it encompasses the G1, S, and G2 phases of the cell cycle.

References

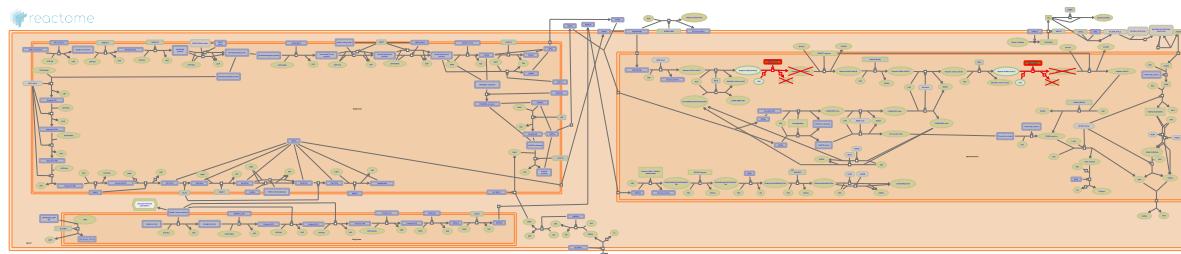
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Date	Action	Author
2018-07-10	Reviewed	Manfredi JJ
2021-09-10	Modified	Weiser JD

6 submitted entities found in this pathway, mapping to 9 Reactome entities

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1460	P67870	23133	O00444, Q9UPP1-1, Q9UPP1-2, Q9UPP1-3	5515	P67775
55869	Q9BY41-1	5885	O60216	8243	Q14683

24. MPS IIIA - Sanfilippo syndrome A ([R-HSA-2206307](#))



Diseases: mucopolysaccharidosis III.

Mucopolysaccharidosis III (MPS III, Sanfilippo syndrome) was described in 1963 by a pediatrician named Sylvester Sanfilippo (J. Pediat. 63: 837-838, 1963, no reference). Mucopolysaccharidosis IIIA (MPS IIIA, Sanfilippo syndrome A, MIM:252900) is a rare, autosomal recessive lysosomal storage disease characterised by severe CNS degeneration in early childhood leading to death between 10 and 20 years of age. A deficiency of the enzyme N-sulphoglucosamine sulphohydrolase (SGSH, MIM:605270), which normally hydrolyses the sulfate group from the terminal N-sulphoglucosamine residue of heparan sulfate (HS), leads to the build-up of HS in cells and tissues and its presence in urine (van de Kamp et al. 1981, Yogalingam & Hopwood 2001, de Ruijter et al. 2011). The gene encoding N-sulfoglucosamine sulfohydrolase, SGSH, was cloned in 1995 (Scott et al. 1995) and, later, shown to contain 8 exons spanning approximately 11 kb (Karageorgos et al. 1996).

References

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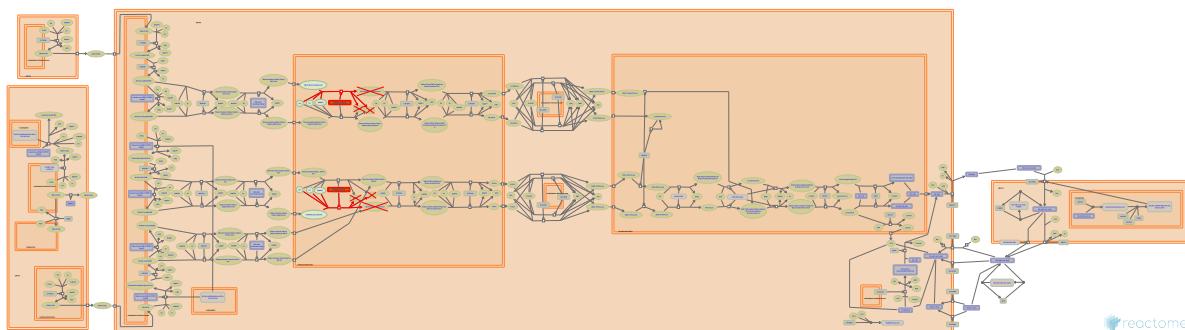
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Date	Action	Author
2012-04-26	Edited	Jassal B
2012-04-26	Authored	Jassal B
2012-04-26	Created	Jassal B
2012-08-27	Reviewed	Alves S, Matos L, Coutinho MF
2018-01-29	Modified	Jassal B

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

Input	UniProt Id
6448	P51688

25. Defective CYP27A1 causes CTX (R-HSA-5578996)



Diseases: cerebrotendinous xanthomatosis.

CYP27A1, a mitochondrial matrix sterol hydroxylase, catalyses the 27-hydroxylation of side-chains of sterol intermediates (Cali et al. 1991). In the bile acid synthesis pathway, CYP27A1 catalyses the first step in the oxidation of the side chain of sterol intermediates such as cholestane-triols (Pikuleva et al. 1998). Defects in CYP27A1 can cause Cerebrotendinous xanthomatosis (CTX; MIM:213700), a rare sterol storage disorder. Decreased bile acid production results in the accumulation of sterol intermediates in many tissues, including brain. The disorder is characterised by progressive neurologic dysfunction, premature atherosclerosis and cataracts (Gallus et al. 2006).

References

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Edit history

Date	Action	Author
2014-06-06	Edited	Jassal B
2014-06-06	Authored	Jassal B
2014-06-06	Created	Jassal B
2014-11-03	Reviewed	Nakaki T
2021-01-21	Modified	Jassal B

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

Input	UniProt Id
1593	Q02318

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.

62 of the submitted entities were found, mapping to 81 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
10075	Q7Z6Z7	1024	P49336	11133	Q9Y664
1120	Q9Y259	122553	Q86SZ2	1460	P67870
1496	P45983	150094	P57059	1593	Q02318
1756	Q9Y2C9	1917	Q05639	200424	O43151
220	P47895	22845	Q9UPQ8	22907	P78357
23133	Q9UPP1-1, Q9UPP1-2, Q9UPP1-3	2556	P54762	2590	P16233
26173	Q16558	2628	P50440	29929	Q9Y672
3054	Q15166	3198	P25929	348980	O60741
4784	Q14938	4915	Q16620	4952	Q01968
5058	Q13153	5080	P26367	5095	P05165
51132	Q9NVW2	51412	O94805	5296	O00459
54806	O95757	5515	P67775	55553	P35712
55869	Q9BY41-1	5587	Q15139	56937	Q969W9
5879	P63000	5885	O60216	5898	P11233
6009	Q15382	6095	P35398	6448	P51688
6506	P43004	6844	P63027	6857	P21579
6872	P21675	7508	Q01831	7528	P25490
816	P36543	8243	Q14683	84628	Q96CW9
8621	Q14004	8812	O75909	8905	P56377
8924	O95714	8936	Q92558	9416	Q9BUQ8
95	Q03154	9681	O75140		

7. Identifiers not found

These 19 identifiers were not found neither mapped to any entity in Reactome.

113246	220296	23241	254065	4858	50651	51319	5455
55773	57231	57666	57688	63035	6899	79853	80185
80232	80856	9758					