



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 78 on 30/11/2021. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTEzMzAxMzQ5MjJfNjAwMw%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
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:

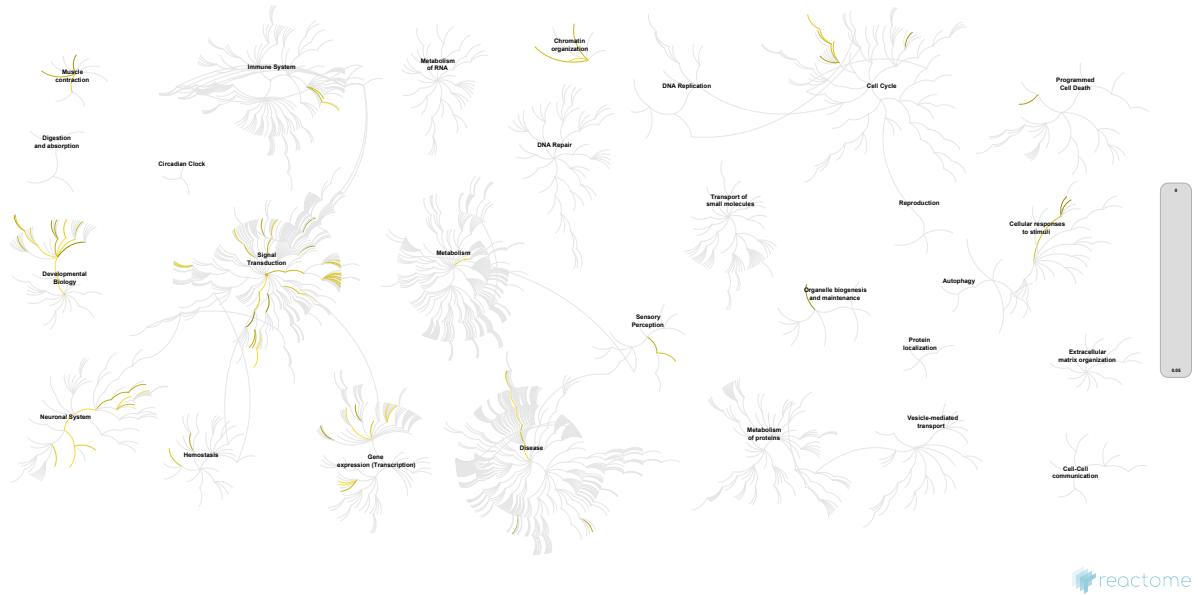
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 172 out of 219 identifiers in the sample were found in Reactome, where 978 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 MjAyMTEzMzAxMzQ5MjJfNjAwMw%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
Neuronal System	26 / 489	0.034	3.90e-06	0.002	92 / 216	0.016
Axon guidance	29 / 585	0.041	4.07e-06	0.002	100 / 298	0.022
Post-transcriptional silencing by small RNAs	4 / 7	4.91e-04	1.21e-05	0.003	3 / 3	2.21e-04
Nervous system development	29 / 621	0.044	1.24e-05	0.003	102 / 324	0.024
Semaphorin interactions	8 / 71	0.005	8.49e-05	0.017	27 / 41	0.003
Protein-protein interactions at synapses	9 / 93	0.007	9.76e-05	0.017	17 / 33	0.002
Neurexins and neuroligins	7 / 60	0.004	1.91e-04	0.028	13 / 19	0.001
Transmission across Chemical Synapses	17 / 343	0.024	4.26e-04	0.051	73 / 163	0.012
NCAM signaling for neurite out-growth	7 / 70	0.005	4.77e-04	0.051	12 / 23	0.002
MAPK family signaling cascades	18 / 380	0.027	4.92e-04	0.051	21 / 122	0.009
Competing endogenous RNAs (ceRNAs) regulate PTEN translation	4 / 19	0.001	5.50e-04	0.052	11 / 11	8.10e-04
Neurotransmitter receptors and postsynaptic signal transmission	13 / 232	0.016	6.69e-04	0.058	61 / 109	0.008
Small interfering RNA (siRNA) biogenesis	3 / 9	6.31e-04	7.57e-04	0.061	5 / 5	3.68e-04
Transcriptional Regulation by MECP2	8 / 100	0.007	8.18e-04	0.061	10 / 77	0.006
FGFR1 mutant receptor activation	5 / 39	0.003	0.001	0.068	18 / 25	0.002
Regulation of MECP2 expression and activity	5 / 39	0.003	0.001	0.068	4 / 14	0.001
Chromatin modifying enzymes	13 / 256	0.018	0.002	0.093	20 / 85	0.006
Chromatin organization	13 / 256	0.018	0.002	0.093	20 / 85	0.006
Unblocking of NMDA receptors, glutamate binding and activation	4 / 27	0.002	0.002	0.109	5 / 5	3.68e-04
Regulation of PTEN mRNA translation	4 / 29	0.002	0.003	0.134	24 / 24	0.002
Signaling by FGFR1 in disease	5 / 49	0.003	0.003	0.138	28 / 35	0.003
Sema4D in semaphorin signaling	4 / 31	0.002	0.003	0.146	10 / 13	9.58e-04
Long-term potentiation	4 / 31	0.002	0.003	0.146	3 / 7	5.16e-04
Regulation of RUNX1 Expression and Activity	4 / 32	0.002	0.004	0.157	11 / 19	0.001

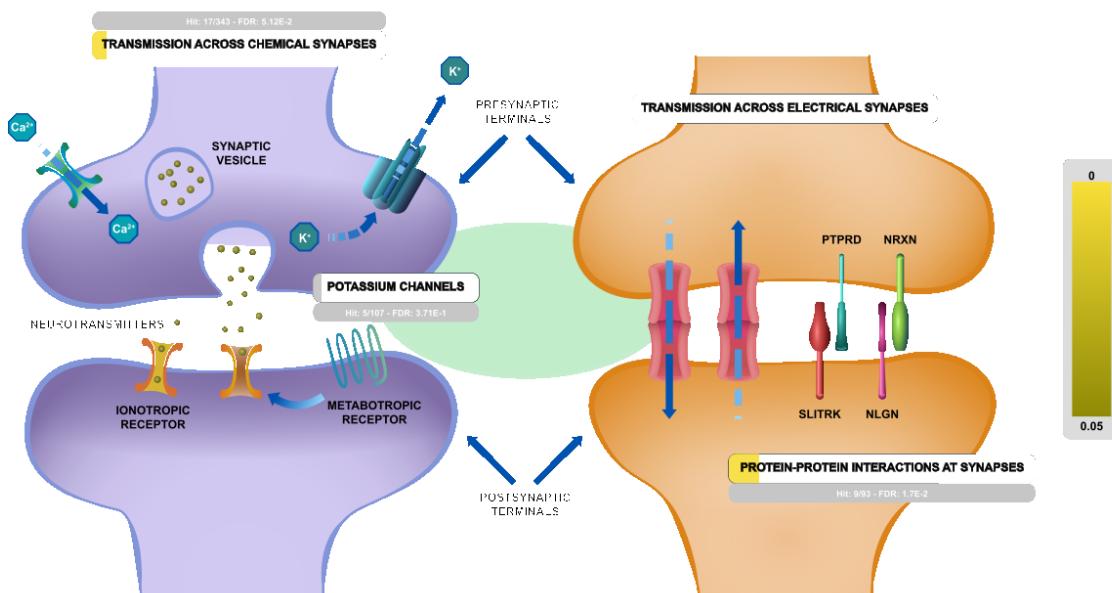
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Diseases of signal transduction by growth factor receptors and second messengers	19 / 498	0.035	0.004	0.161	111 / 484	0.036

* 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. Neuronal System (R-HSA-112316)



The human brain contains at least 100 billion neurons, each with the ability to influence many other cells. Clearly, highly sophisticated and efficient mechanisms are needed to enable communication among this astronomical number of elements. This communication occurs across synapses, the functional connection between neurons. Synapses can be divided into two general classes: electrical synapses and chemical synapses. Electrical synapses permit direct, passive flow of electrical current from one neuron to another. The current flows through gap junctions, specialized membrane channels that connect the two cells. Chemical synapses enable cell-to-cell communication using neurotransmitter release. Neurotransmitters are chemical agents released by presynaptic neurons that trigger a secondary current flow in postsynaptic neurons by activating specific receptor molecules. Neurotransmitter secretion is triggered by the influx of Ca²⁺ through voltage-gated channels, which gives rise to a transient increase in Ca²⁺ concentration within the presynaptic terminal. The rise in Ca²⁺ concentration causes synaptic vesicles (the presynaptic organelles that store neurotransmitters) to fuse with the presynaptic plasma membrane and release their contents into the space between the pre- and postsynaptic cells.

References

Fitzpatrick D, Augustine DJ, Katz LC, Williams JM, Purves D, McNamara JO & LaMantia AS (2001). *Neuroscience 2nd Edition*.

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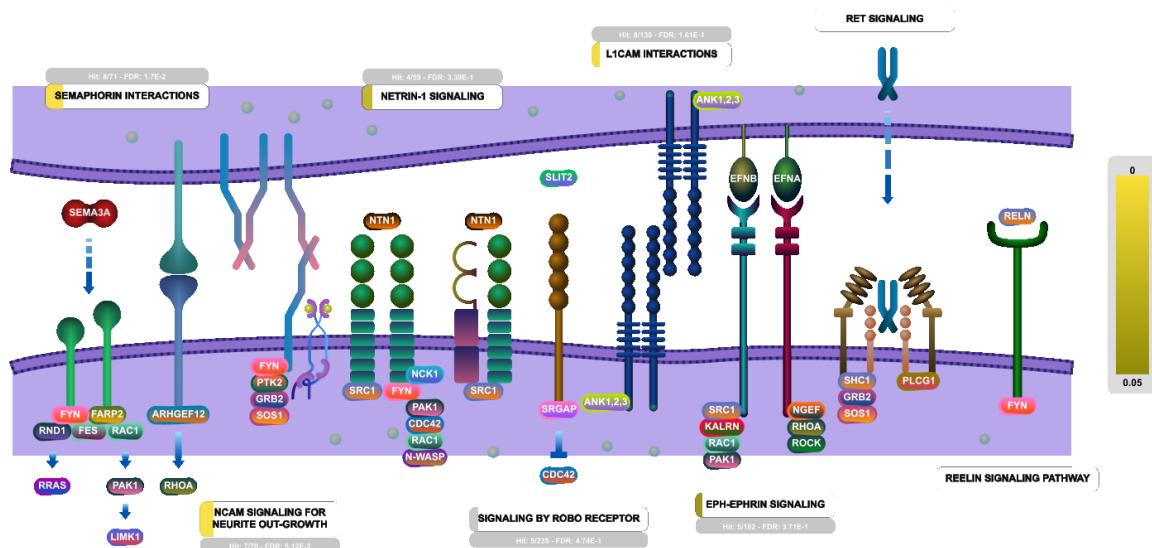
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2004-04-22	Created	Joshi-Tope G
2005-11-10	Edited	Gillespie ME

Date	Action	Author
2005-11-10	Authored	Gillespie ME
2021-09-10	Modified	Weiser JD

25 submitted entities found in this pathway, mapping to 26 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1012	Q05940	109	O60266	1139	P36544
1740	Q15700	22871	Q8N2Q7	23236	Q9NQ66
2567	Q99928	26050	O94991	2890	P42261
2898	Q13002	2901	Q16478	2902	Q05586
2903	Q12879	29998	P46098	3766	P78508
3785	O43526, P61764	3790	Q9BQ31	43	P22303
50944	Q9Y566	547	Q92953	552	Q9NSA2
5579	P05771	6531	Q01959	783	Q08289
9229	O14490				

2. Axon guidance (R-HSA-422475)



Axon guidance / axon pathfinding is the process by which neurons send out axons to reach the correct targets. Growing axons have a highly motile structure at the growing tip called the growth cone, which senses the guidance cues in the environment through guidance cue receptors and responds by undergoing cytoskeletal changes that determine the direction of axon growth.

Guidance cues present in the surrounding environment provide the necessary directional information for the trip. These extrinsic cues have been divided into attractive or repulsive signals that tell the growth cone where and where not to grow.

Genetic and biochemical studies have led to the identification of highly conserved families of guidance molecules and their receptors that guide axons. These include netrins, Slits, semaphorins, and ephrins, and their cognate receptors, DCC and or uncoordinated-5 (UNC5), roundabouts (Robo), neuropilin and Eph. In addition, many other classes of adhesion molecules are also used by growth cones to navigate properly which include NCAM and L1CAM.

For review of axon guidance, please refer to Russel and Bashaw 2018, Chedotal 2019, Suter and Jaworski 2019).

Axon guidance cues and their receptors are implicated in cancer progression (Biankin et al. 2012), where they likely contribute to cell migration and angiogenesis (reviewed by Mehlen et al. 2011).

References

- Russell SA & Bashaw GJ (2018). Axon guidance pathways and the control of gene expression. *Dev. Dyn.*, 247, 571-580. [🔗](#)
- Jaworski A & Suter TACS (2019). Cell migration and axon guidance at the border between central and peripheral nervous system. *Science*, 365. [🔗](#)
- Chédotal A (2019). Roles of axon guidance molecules in neuronal wiring in the developing spinal cord. *Nat. Rev. Neurosci.*, 20, 380-396. [🔗](#)

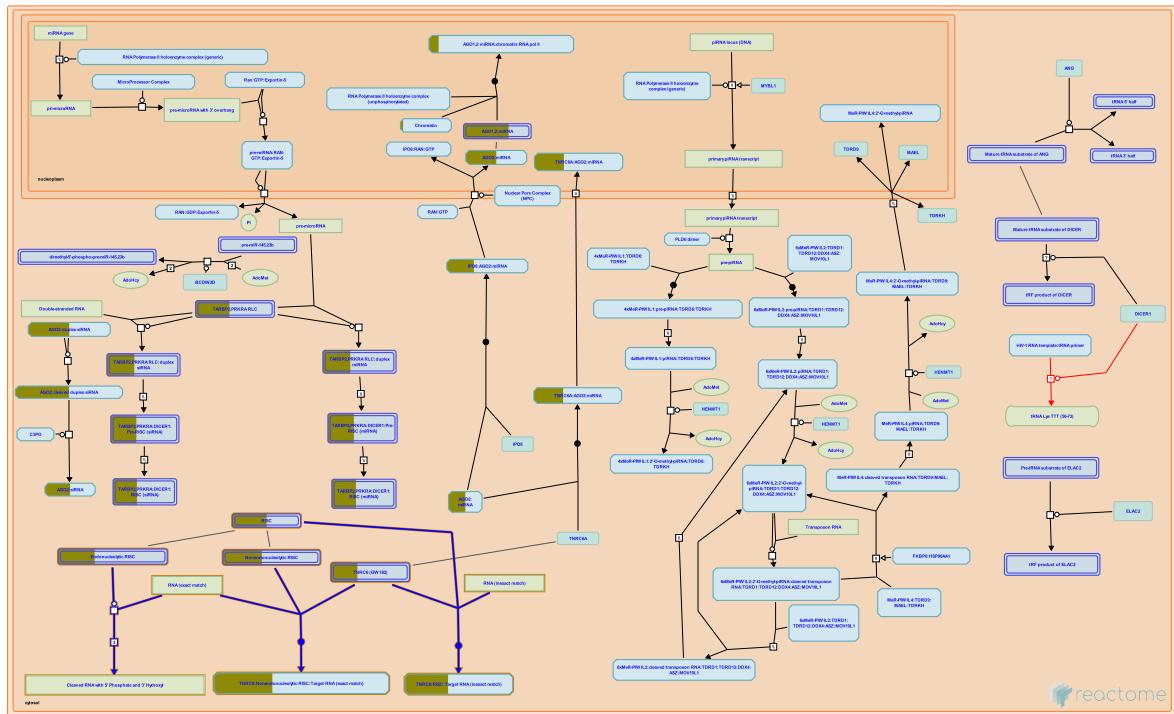
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2009-05-26	Reviewed	Walmod PS, Maness PF
2009-05-29	Edited	Garapati P V
2009-05-29	Authored	Garapati P V
2009-05-31	Created	Garapati P V
2021-09-10	Modified	Weiser JD

28 submitted entities found in this pathway, mapping to 29 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
116986	Q99490	1501	P53778	1523	O75582
1630	P43146	2260	P11362-1	23332	Q7Z460
27255	Q9UQ52	2902	Q05586	3690	P05106
3785	O43526	3912	P07942	4233	P08581
4627	P35579	4628	P35580	4650	Q13459
5062	Q13177	51107	Q96BI3	5364	O43157
6092	Q9HCK4	6335	Q15858	6711	Q01082
7225	Q9Y210	776	Q01668	783	Q08289
8128	Q92186	8912	O95180	9037	Q13591
91584	O60486, Q9HCM2				

3. Post-transcriptional silencing by small RNAs ([R-HSA-426496](#))



Cellular compartments: cytosol.

Small RNAs act with components of the RNA-induced silencing complex (RISC) to post-transcriptionally repress expression of mRNAs (reviewed in Nowotny and Yang 2009, Chua et al. 2009). Two mechanisms exist: 1) cleavage of target RNAs by complexes containing Argonaute2 (AGO2, EIF2C2) and a guide RNA that exactly matches the target mRNA and 2) inhibition of translation of target RNAs by complexes containing AGO2 and an inexactly matching guide RNA or by complexes containing a nonendonucleolytic Argonaute (AGO1 (EIF2C1), AGO3 (EIF2C3), or AGO4 (EIF2C4)) and a guide RNA of exact or inexact match. Small interfering RNAs (siRNAs) and microRNAs (miRNAs) can serve as guide RNAs in both types of mechanism.

RNAi also appears to direct chromatin modifications that cause transcriptional gene silencing (reviewed in Verdel et al. 2009).

References

- Filipowicz W, Pillai RS & Bhattacharyya SN (2007). Repression of protein synthesis by miRNAs: how many mechanisms?. *Trends Cell Biol*, 17, 118-26. 

Liu J, Hannon GJ, Parker R & Valencia-Sanchez MA (2006). Control of translation and mRNA degradation by miRNAs and siRNAs. *Genes Dev*, 20, 515-24. 

van den Berg A, Mols J & Han J (2008). RISC-target interaction: cleavage and translational suppression. *Biochim Biophys Acta*, 1779, 668-77. 

Izaurrealde E & Jonas S (2015). Towards a molecular understanding of microRNA-mediated gene silencing. *Nat. Rev. Genet.*, 16, 421-33. 

Peters L & Meister G (2007). Argonaute proteins: mediators of RNA silencing. *Mol Cell*, 26, 611-23. 

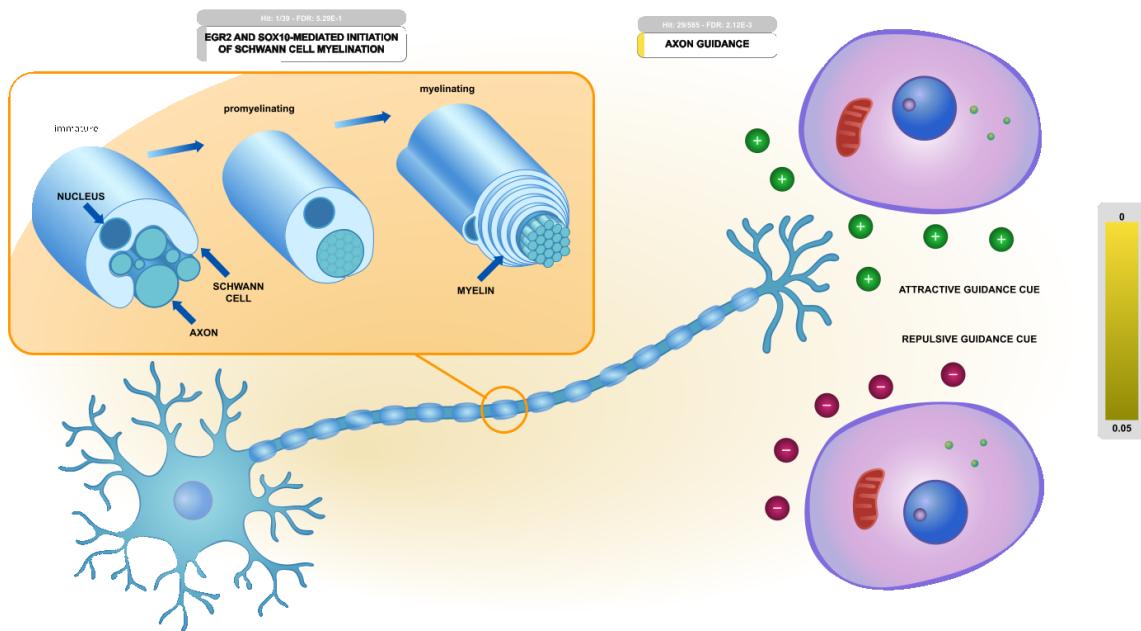
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Date	Action	Author
2009-06-10	Edited	May B
2009-06-10	Authored	May B
2009-06-17	Created	May B
2012-02-11	Reviewed	Tomari Y
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
192670	Q9HCK5	23112	Q9UPQ9
26523	Q9UL18	27161	Q9UKV8

4. 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. [\[CrossRef\]](#)
- Kriegstein A & Alvarez-Buylla A (2009). The glial nature of embryonic and adult neural stem cells. *Annu. Rev. Neurosci.*, 32, 149-84. [\[CrossRef\]](#)
- Christian KM, Ming GL, Yao B, Song H, Jin P & He C (2016). Epigenetic mechanisms in neurogenesis. *Nat. Rev. Neurosci.*, 17, 537-49. [\[CrossRef\]](#)

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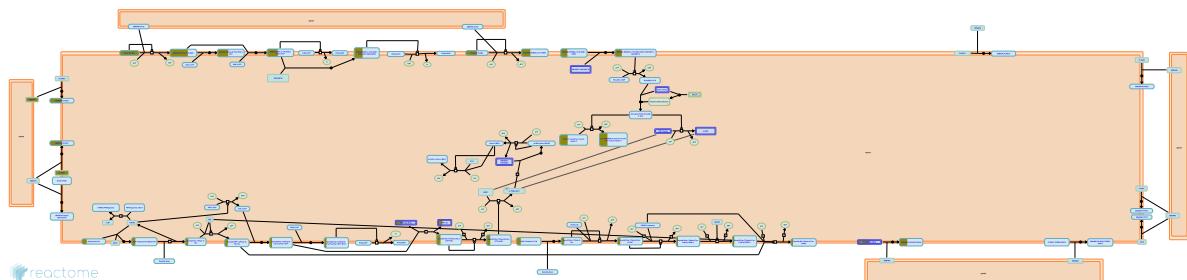
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2020-01-23	Reviewed	Orlic-Milacic M
2020-01-31	Edited	Rothfels K
2020-01-31	Authored	Rothfels K
2020-01-31	Created	Rothfels K
2021-09-10	Modified	Weiser JD

28 submitted entities found in this pathway, mapping to 29 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
116986	Q99490	1501	P53778	1523	O75582
1630	P43146	2260	P11362-1	23332	Q7Z460
27255	Q9UQ52	2902	Q05586	3690	P05106
3785	O43526	3912	P07942	4233	P08581

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
4627	P35579	4628	P35580	4650	Q13459
5062	Q13177	51107	Q96BI3	5364	O43157
6092	Q9HCK4	6335	Q15858	6711	Q01082
7225	Q9Y210	776	Q01668	783	Q08289
8128	Q92186	8912	O95180	9037	Q13591
91584	O60486, Q9HCM2				

5. Semaphorin interactions (R-HSA-373755)



Semaphorins are a large family of cell surface and secreted guidance molecules divided into eight classes on the basis of their structures. They all have an N-terminal conserved sema domain. Semaphorins signal through multimeric receptor complexes that include other proteins such as plexins and neuropilins.

References

- Verhaagen J & Pasterkamp RJ (2006). Semaphorins in axon regeneration: developmental guidance molecules gone wrong?. *Philos Trans R Soc Lond B Biol Sci*, 361, 1499-511. [\[link\]](#)
- Dickson BJ (2002). Molecular mechanisms of axon guidance. *Science*, 298, 1959-64. [\[link\]](#)
- Koncina E, Bagnard D, Roth L & Gonthier B (2007). Role of semaphorins during axon growth and guidance. *Adv Exp Med Biol*, 621, 50-64. [\[link\]](#)
- Zhou Y, Pasterkamp RJ & Gunput RA (2008). Semaphorin signaling: progress made and promises ahead. *Trends Biochem Sci*, 33, 161-70. [\[link\]](#)
- Pasterkamp RJ & Kolodkin AL (2003). Semaphorin junction: making tracks toward neural connectivity. *Curr Opin Neurobiol*, 13, 79-89. [\[link\]](#)

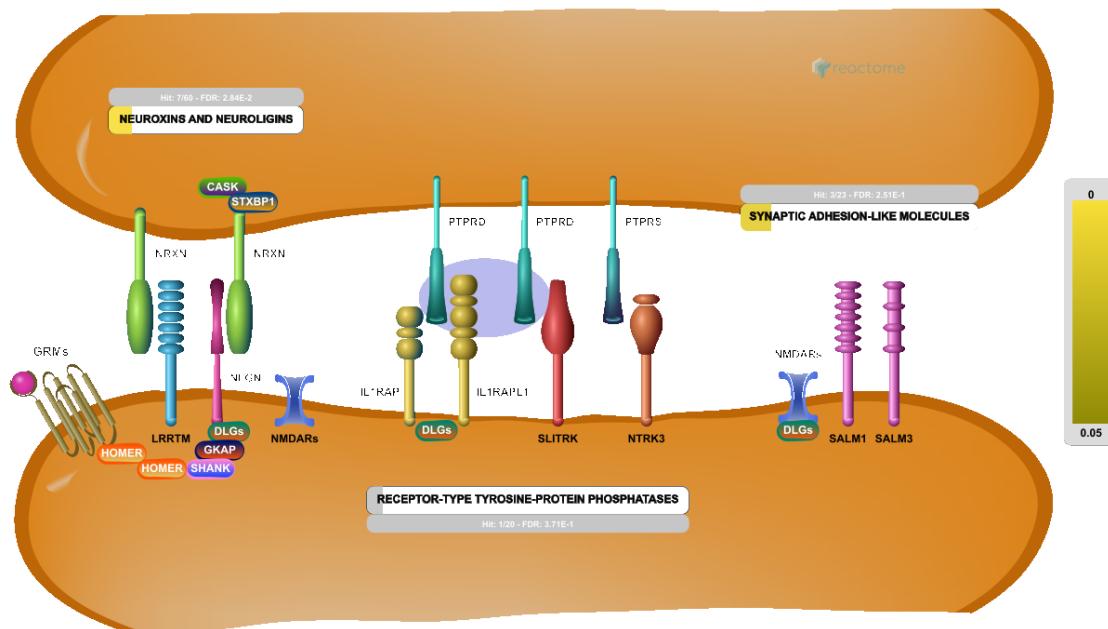
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2009-03-23	Authored	Garapati P V
2009-09-02	Reviewed	Kumanogoh A, Kikutani H
2021-09-10	Modified	Weiser JD

7 submitted entities found in this pathway, mapping to 8 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
4233	P08581	4627	P35579	4628	P35580
5062	Q13177	5364	O43157	9037	Q13591
91584	O60486, Q9HCM2				

6. Protein-protein interactions at synapses (R-HSA-6794362)



Cellular compartments: plasma membrane, cytosol.

Synapses constitute highly specialized sites of asymmetric cell-cell adhesion and intercellular communication. Its formation involves the recruitment of presynaptic and postsynaptic molecules at newly formed contacts. Synapse assembly and maintenance invokes heterophilic presynaptic and postsynaptic transmembrane proteins that bind each other in the extracellular space and recruit additional proteins via their intracellular domains. Members of the cadherin and immunoglobulin (Ig) superfamilies are thought to mediate this function. Several molecules, including synaptic cell-adhesion molecule (SynCAM), N-cadherin, neural cell-adhesion molecule (NCAM), Eph receptor tyrosine kinases, and neuroligins and neurexins, have been implicated in synapse formation and maintenance (Dean & Dresbach 2006, Craig et al. 2006, Craig & Kang 2007, Sudhof 2008).

References

- McClelland AC, Dalva MB & Kayser MS (2007). Cell adhesion molecules: signalling functions at the synapse. *Nat. Rev. Neurosci.*, 8, 206-20. [View](#)
- Dresbach T & Dean C (2006). Neuroligins and neurexins: linking cell adhesion, synapse formation and cognitive function. *Trends Neurosci.*, 29, 21-9. [View](#)
- Südhof TC (2008). Neuroligins and neurexins link synaptic function to cognitive disease. *Nature*, 455, 903-11. [View](#)

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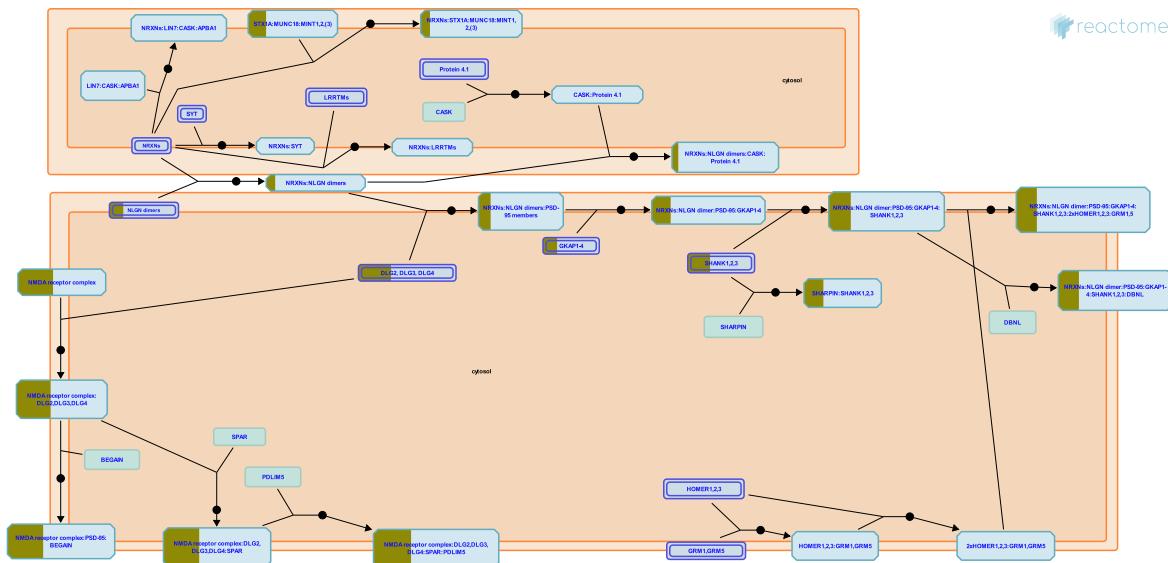
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2015-09-04	Authored	Garapati P V
2015-09-04	Created	Garapati P V
2015-11-09	Reviewed	Washbourne P

Date	Action	Author
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1740	Q15700	22871	Q8N2Q7	26050	O94991
2890	P42261	2902	Q05586	2903	Q12879
3785	P61764	50944	Q9Y566	9229	O14490

7. Neurexins and neuroligins (R-HSA-6794361)



Neurexins (NRXNs) and neuroligins (NLGNs) are best characterized synaptic cell-adhesion molecules. They are part of excitatory glutamatergic and inhibitory GABAergic synapses in mammalian brain, mediate trans-synaptic signaling, and shape neural network properties by specifying synaptic functions. As cell-adhesion molecules, Nrxns and Nlgns probably function by binding to each other and by interacting with intracellular PDZ-domain proteins, but the precise mechanisms involved and their relation to synaptic transmission remain unclear. The binding of Nrxns and Nlgns to their partners, helps to align the pre-synaptic release machinery and post-synaptic receptors. The importance of neurexins and neuroligins for synaptic function is evident from the dramatic deficits in synaptic transmission in mice lacking Nrxns or Nlgns. In humans, alterations in Nrxns or Nlgns genes are implicated in autism and other cognitive diseases, connecting synaptic cell adhesion to cognition and its disorders (Sudhof 2008, Craig et al. 2006, Craig & Kang 2007).

References

- Bang ML & Owczarek S (2013). A matter of balance: role of neurexin and neuroligin at the synapse. *Neurochem. Res.*, 38, 1174-89. [View](#)
- Papadopoulos T, Brose N, Tuffy LP & Krueger DD (2012). The role of neurexins and neuroligins in the formation, maturation, and function of vertebrate synapses. *Curr. Opin. Neurobiol.*, 22, 412-22. [View](#)
- Craig AM & Kang Y (2007). Neurexin-neuroligin signaling in synapse development. *Curr. Opin. Neurobiol.*, 17, 43-52. [View](#)
- Wright GJ & Washbourne P (2011). Neurexins, neuroligins and LRRM: synaptic adhesion getting fishy. *J. Neurochem.*, 117, 765-78. [View](#)
- McClelland AC, Dalva MB & Kayser MS (2007). Cell adhesion molecules: signalling functions at the synapse. *Nat. Rev. Neurosci.*, 8, 206-20. [View](#)

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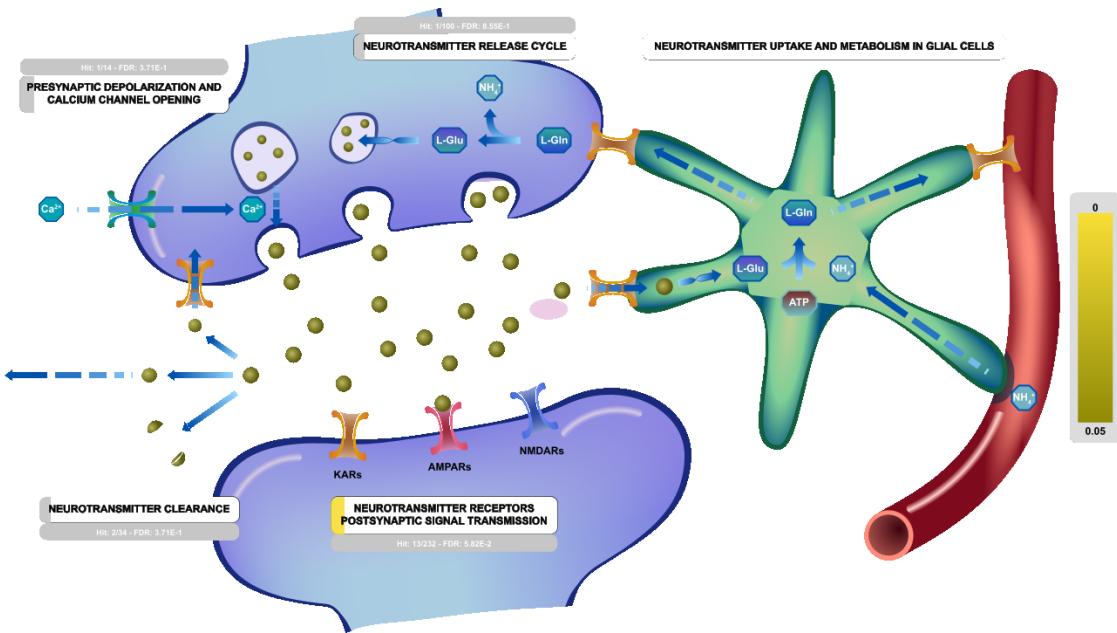
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Date	Action	Author
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2015-09-04	Created	Garapati P V
2015-11-09	Reviewed	Washbourne P
2021-09-10	Modified	Weiser JD

7 submitted entities found in this pathway, mapping to 7 Reactome entities

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1740	Q15700	22871	Q8N2Q7	2902	Q05586
2903	Q12879	3785	P61764	50944	Q9Y566
9229	O14490				

8. Transmission across Chemical Synapses (R-HSA-112315)



Chemical synapses are specialized junctions that are used for communication between neurons, neurons and muscle or gland cells. The synapse involves a presynaptic neuron and a postsynaptic neuron, muscle cell or glad cell. The pre and the postsynaptic cell are separated by a gap (space) of 20 to 40 nm called the synaptic cleft. The signals pass in a single direction from the presynaptic to postsynaptic neuron (cell). The presynaptic neuron communicates via the release of neurotransmitter which bind the receptors on the postsynaptic cell. The process is initiated when an action potential invades the terminal membrane of the presynaptic neuron.

Action potentials occur in electrically excitable cells such as neurons and muscles and endocrine cells. They are initiated by the transient opening of voltage dependent sodium channels, causing a rapid, large depolarization of membrane potentials that spread along the axon membrane.

When action potentials arrive at the synaptic terminals, depolarization in membrane potential leads to the opening of voltage gated calcium channels located on the presynaptic membrane. The external Ca²⁺ concentration is approximately 10-3 M while the internal Ca²⁺ concentration is approximately 10-7 M. Opening of calcium channels causes a rapid influx of Ca²⁺ into the presynaptic terminal. The elevated presynaptic Ca²⁺ concentration allows synaptic vesicles to fuse with the plasma membrane of the presynaptic neuron and release their contents, neurotransmitters, into the synaptic cleft. These diffuse across the synaptic cleft and bind to specific receptors on the membrane of the postsynaptic cells. Activation of postsynaptic receptors upon neurotransmitter binding can lead to a multitude of effects in the postsynaptic cell, such as changing the membrane potential and excitability, and triggering intracellular signaling cascades.

References

Fitzpatrick D, Augustine DJ, Katz LC, Williams JM, Purves D, McNamara JO & LaMantia AS (2001). *Neuroscience 2nd Edition*.

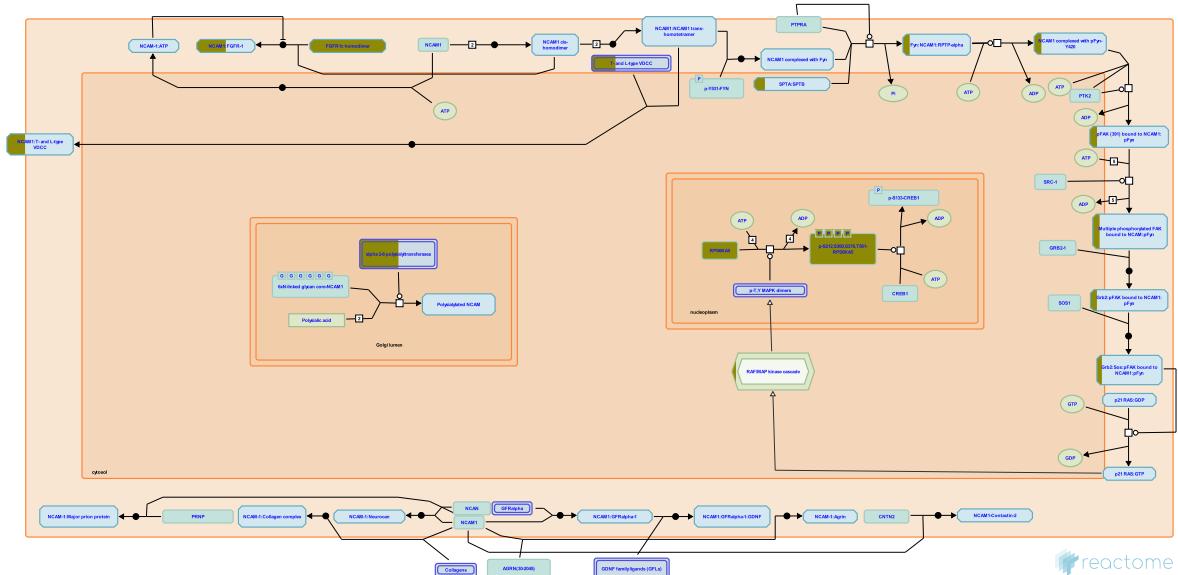
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2008-01-14	Authored	Mahajan SS
2008-12-02	Reviewed	Restituito S, Kavalali E
2020-01-24	Reviewed	Wen H
2021-09-10	Modified	Weiser JD

17 submitted entities found in this pathway, mapping to 17 Reactome entities

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2890	P42261	2898	Q13002	2901	Q16478
2902	Q05586	2903	Q12879	29998	P46098
3766	P78508	43	P22303	5579	P05771
6531	Q01959	783	Q08289		

9. NCAM signaling for neurite out-growth (R-HSA-375165)



Cellular compartments: plasma membrane.

The neural cell adhesion molecule, NCAM, is a member of the immunoglobulin (Ig) superfamily and is involved in a variety of cellular processes of importance for the formation and maintenance of the nervous system. The role of NCAM in neural differentiation and synaptic plasticity is presumed to depend on the modulation of intracellular signal transduction cascades. NCAM based signaling complexes can initiate downstream intracellular signals by at least two mechanisms: (1) activation of FGFR and (2) formation of intracellular signaling complexes by direct interaction with cytoplasmic interaction partners such as Fyn and FAK. Tyrosine kinases Fyn and FAK interact with NCAM and undergo phosphorylation and this transiently activates the MAPK, ERK 1 and 2, cAMP response element binding protein (CREB) and transcription factors ELK and NFkB. CREB activates transcription of genes which are important for axonal growth, survival, and synaptic plasticity in neurons.

NCAM1 mediated intracellular signal transduction is represented in the figure below. The Ig domains in NCAM1 are represented in orange ovals and Fn domains in green squares. The tyrosine residues susceptible to phosphorylation are represented in red circles and their positions are numbered. Phosphorylation is represented by red arrows and dephosphorylation by yellow. Ig, Immunoglobulin domain; Fn, Fibronectin domain; Fyn, Proto-oncogene tyrosine-protein kinase Fyn; FAK, focal adhesion kinase; RPTPalpha, Receptor-type tyrosine-protein phosphatase; Grb2, Growth factor receptor-bound protein 2; SOS, Son of sevenless homolog; Raf, RAF proto-oncogene serine/threonine-protein kinase; MEK, MAPK and ERK kinase; ERK, Extracellular signal-regulated kinase; MSK1, Mitogen and stress activated protein kinase 1; CREB, Cyclic AMP-responsive element-binding protein; CRE, cAMP response elements.

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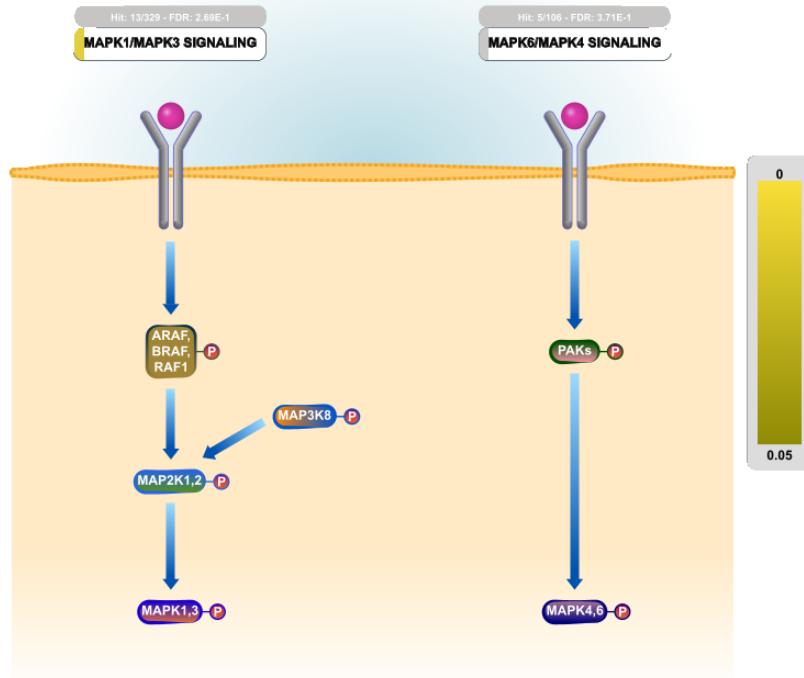
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Date	Action	Author
2008-08-11	Created	Garapati P V
2009-02-24	Edited	Garapati P V
2009-02-24	Authored	Garapati P V
2009-05-26	Reviewed	Walmod PS, Maness PF
2021-09-10	Modified	Weiser JD

7 submitted entities found in this pathway, mapping to 7 Reactome entities

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1523	O75582	2260	P11362-1	6711	Q01082
776	Q01668	783	Q08289	8128	Q92186
8912	O95180				

10. MAPK family signaling cascades (R-HSA-5683057)



The mitogen activated protein kinases (MAPKs) are a family of conserved protein serine threonine kinases that respond to varied extracellular stimuli to activate intracellular processes including gene expression, metabolism, proliferation, differentiation and apoptosis, among others.

The classic MAPK cascades, including the ERK1/2 pathway, the p38 MAPK pathway, the JNK pathway and the ERK5 pathway are characterized by three tiers of sequentially acting, activating kinases (reviewed in Kryiakis and Avruch, 2012; Cargnello and Roux, 2011). The MAPK kinase kinase kinase (MAPKKK), at the top of the cascade, is phosphorylated on serine and threonine residues in response to external stimuli; this phosphorylation often occurs in the context of an interaction between the MAPKKK protein and a member of the RAS/RHO family of small GTP-binding proteins. Activated MAPKKK proteins in turn phosphorylate the dual-specificity MAPK kinase proteins (MAPKK), which ultimately phosphorylate the MAPK proteins in a conserved Thr-X-Tyr motif in the activation loop.

Less is known about the activation of the atypical families of MAPKs, which include the ERK3/4 signaling cascade, the ERK7 cascade and the NLK cascade. Although the details are not fully worked out, these MAPK proteins don't appear to be phosphorylated downstream of a 3-tiered kinase system as described above (reviewed in Coulombe and Meloche, 2007; Cargnello and Roux, 2011).

Both conventional and atypical MAPKs are proline-directed serine threonine kinases and, once activated, phosphorylate substrates in the consensus P-X-S/T-P site. Both cytosolic and nuclear targets of MAPK proteins have been identified and upon stimulation, a proportion of the phosphorylated MAPKs relocalize from the cytoplasm to the nucleus. In some cases, nuclear translocation may be accompanied by dimerization, although the relationship between these two events is not fully elaborated (reviewed in Kryiakis and Avruch, 2012; Cargnello and Roux, 2011; Plotnikov et al, 2010).

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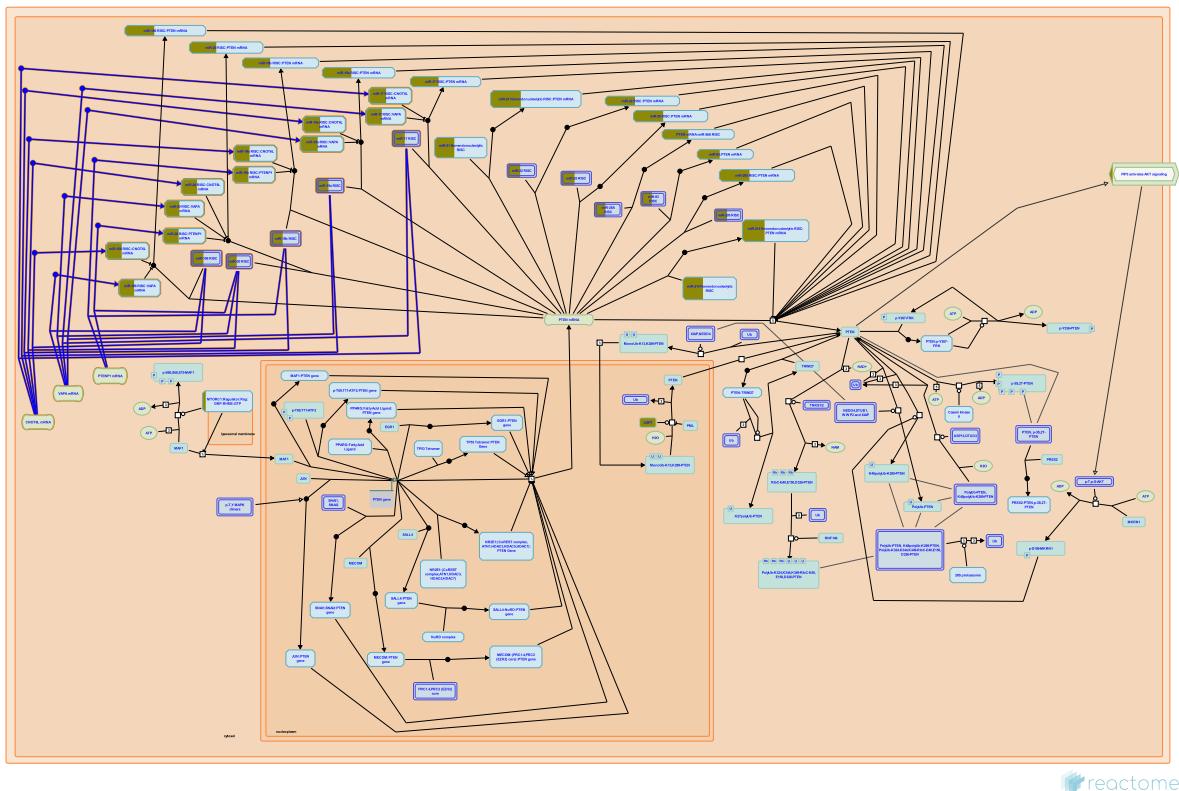
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2015-03-10	Authored	Rothfels K
2015-03-11	Created	Rothfels K
2015-04-29	Reviewed	Roskoski R Jr
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1501	P53778	1740	Q15700	192670	Q9HCK5
2200	Q07817	2260	P11362-1, P11362-19	22866	Q8WXI2
23112	Q9UPQ9	26523	Q9UL18	27161	Q9UKV8
2901	P05231	2902	P08887, Q05586	3690	P05106
4233	P08581	5062	Q13177	5245	P35232
6711	Q01082				

11. Competing endogenous RNAs (ceRNAs) regulate PTEN translation (R-HSA-8948700)



Coding and non-coding RNAs can prevent microRNAs from binding to PTEN mRNA. These RNAs are termed competing endogenous RNAs or ceRNAs. Transcripts of the pseudogene PTENP1 and mRNAs transcribed from SERINC1, VAPA and CNOT6L genes exhibit this activity (Poliseno et al. 2010, Tay et al. 2011, Tay et al. 2014). SERINC1 mRNA will be annotated in this context when additional experimental details become available.

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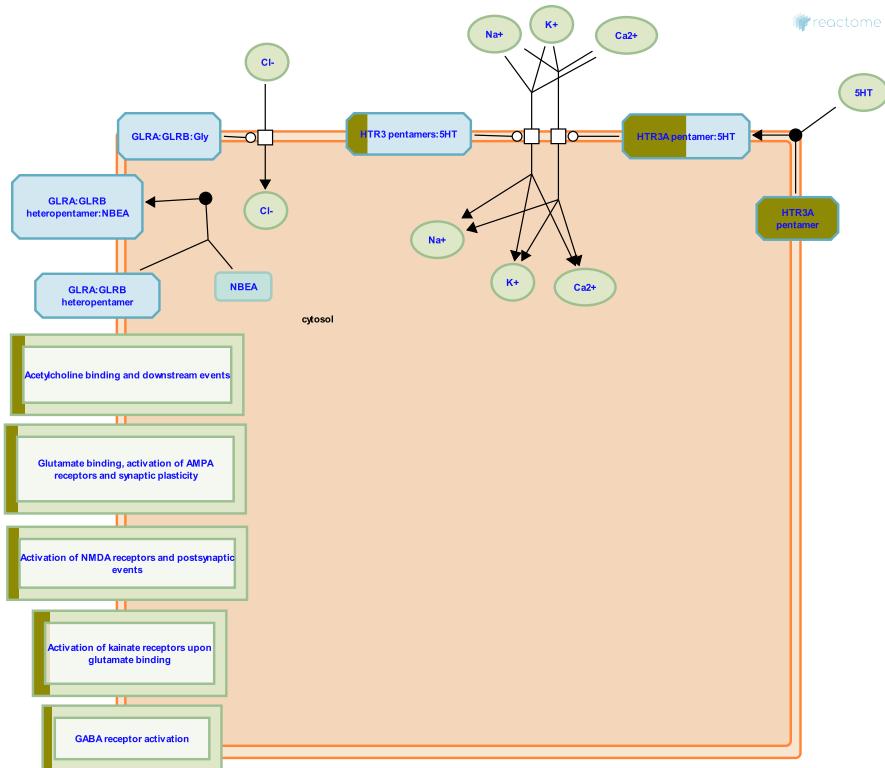
Date	Action	Author
2016-08-11	Authored	Salmena L, Carracedo A
2016-11-03	Authored	Orlic-Milacic M
2016-11-16	Created	Orlic-Milacic M
2017-05-09	Modified	Orlic-Milacic M

Date	Action	Author
2017-05-09	Edited	Orlic-Milacic M

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

Input	UniProt Id	Input	UniProt Id
192670	Q9HCK5	23112	Q9UPQ9
26523	Q9UL18	27161	Q9UKV8

12. Neurotransmitter receptors and postsynaptic signal transmission (R-HSA-112314)



The neurotransmitter in the synaptic cleft released by the pre-synaptic neuron binds specific receptors located on the post-synaptic terminal. These receptors are either ion channels or G protein coupled receptors that function to transmit the signals from the post-synaptic membrane to the cell body.

References

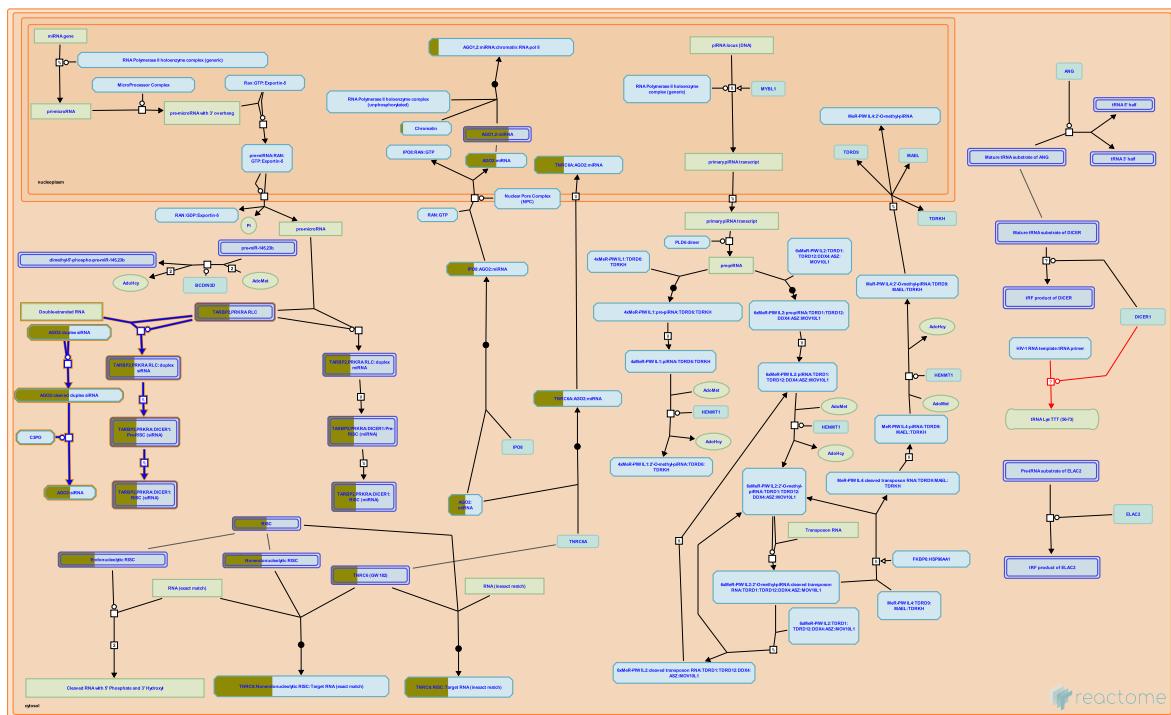
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Date	Action	Author
2004-04-22	Created	Joshi-Tope G
2008-01-14	Authored	Mahajan SS
2008-12-02	Reviewed	Restituito S, Kavalali E
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
109	O60266	1139	P36544	1740	Q15700
23236	Q9NQ66	2567	Q99928	2890	P42261
2898	Q13002	2901	Q16478	2902	Q05586
2903	Q12879	29998	P46098	3766	P78508
5579	P05771				

13. Small interfering RNA (siRNA) biogenesis (R-HSA-426486)



Cellular compartments: cytosol.

Small interfering RNAs (siRNAs) are 21-25 nucleotide single-stranded RNAs produced by cleavage of longer double-stranded RNAs by the enzyme DICER1 within the RISC loading complex containing DICER1, an Argonaute protein, and either TARBP2 or PRKRA (PACT). Typically the long double-stranded substrates originate from viruses or repetitive elements in the genome and the two strands of the substrate are exactly complementary.

After cleavage by DICER1 the 21-25 nucleotide double-stranded product is loaded into an Argonaute protein (humans contain 4 Argonautes) and rendered single-stranded by a mechanism that is not well characterized.

siRNA-loaded AGO2 is predominantly located at the cytosolic face of the rough endoplasmic reticulum and has also been observed in the nucleus.

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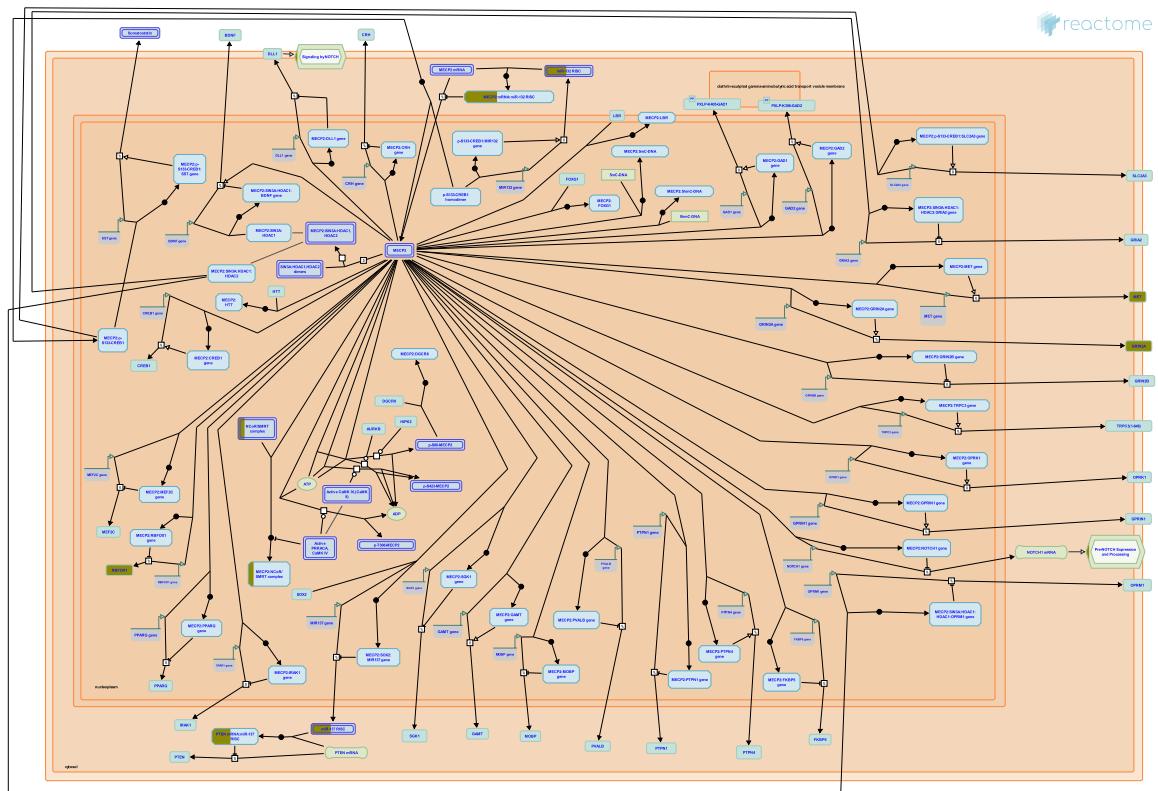
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2009-06-10	Edited	May B
2009-06-10	Authored	May B
2009-06-17	Created	May B
2012-02-11	Reviewed	Tomari Y
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
192670	Q9HCK5	26523	Q9UL18	27161	Q9UKV8

14. 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 (Lividé 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 (Liyo 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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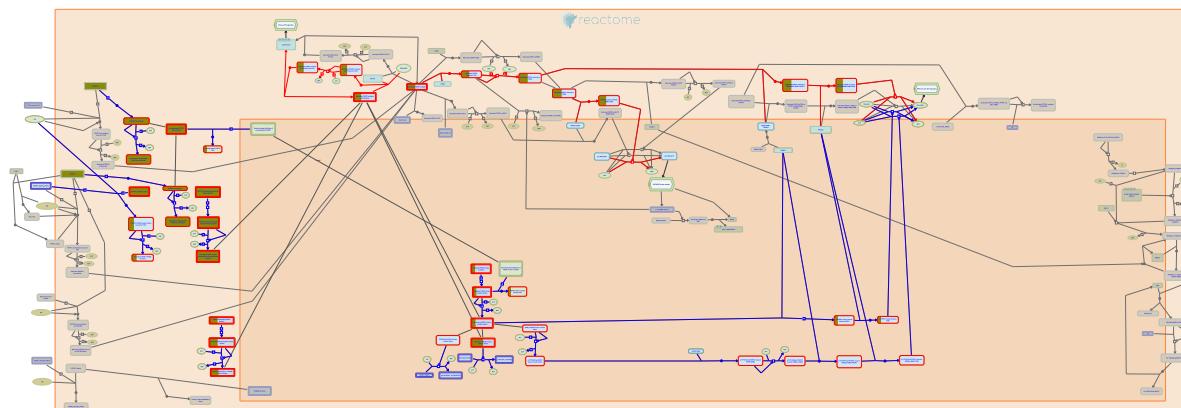
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2017-05-05	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

8 submitted entities found in this pathway, mapping to 8 Reactome entities

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192670	Q9HCK5	23112	Q9UPQ9	26523	Q9UL18

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
27161	Q9UKV8	2903	Q12879	4233	P08581
54715	Q9NWB1	9611	075376		

15. FGFR1 mutant receptor activation (R-HSA-1839124)



Cellular compartments: plasma membrane, extracellular region, cytosol.

Diseases: cancer, bone development disease.

The FGFR1 gene has been shown to be subject to activating mutations, chromosomal rearrangements and gene amplification leading to a variety of proliferative and developmental disorders depending on whether these events occur in the germline or arise somatically (reviewed in Webster and Donoghue, 1997; Burke, 1998; Cunningham, 2007; Wesche, 2011; Greulich and Pollock, 2011). Many of the resulting mutant FGFR1 proteins can dimerize and promote signaling in a ligand-independent fashion, although signal transduction may still be amplified in the presence of ligand (reviewed in Turner and Gross, 2010; Greulich and Pollock, 2011; Wesche et al, 2011).

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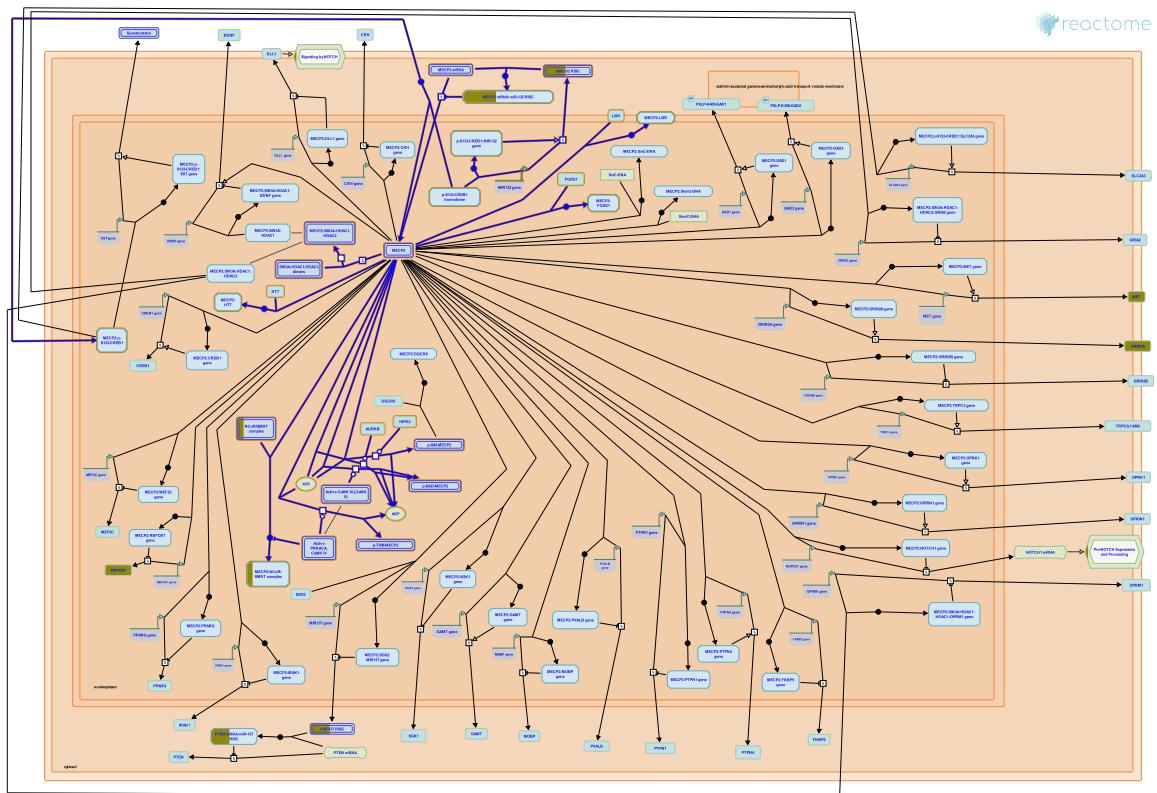
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2011-10-27	Created	Rothfels K
2012-02-10	Authored	Rothfels K
2012-05-15	Reviewed	Ezzat S
2012-05-17	Edited	Rothfels K
2016-01-09	Revised	Rothfels K
2016-01-22	Modified	Rothfels K

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1523	P39880	2260	P11362, P11362-1, P11362-19	7750	Q9UBW7

16. 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).

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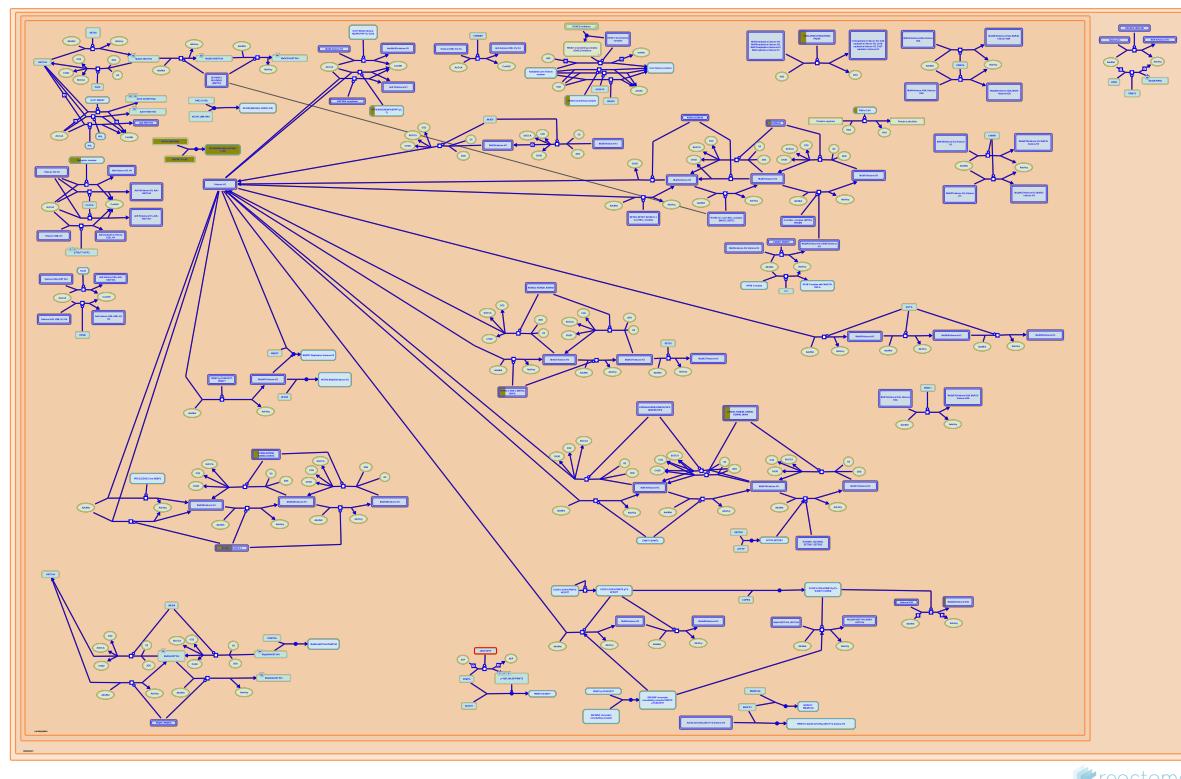
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2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
192670	Q9HCK5	23112	Q9UPQ9	26523	Q9UL18
27161	Q9UKV8	9611	O75376		

17. Chromatin modifying enzymes (R-HSA-3247509)



Eukaryotic DNA is associated with histone proteins and organized into a complex nucleoprotein structure called chromatin. This structure decreases the accessibility of DNA but also helps to protect it from damage. Access to DNA is achieved by highly regulated local chromatin decondensation.

The 'building block' of chromatin is the nucleosome. This contains ~150 bp of DNA wrapped around a histone octamer which consists of two each of the core histones H2A, H2B, H3 and H4 in a 1.65 left-handed superhelical turn (Luger et al. 1997, Andrews & Luger 2011).

Most organisms have multiple genes encoding the major histone proteins. The replication-dependent genes for the five histone proteins are clustered together in the genome in all metazoans. Human replication-dependent histones occur in a large cluster on chromosome 6 termed HIST1, a smaller cluster HIST2 on chromosome 1q21, and a third small cluster HIST3 on chromosome 1q42 (Marzluff et al. 2002). Histone genes are named systematically according to their cluster and location within the cluster.

The 'major' histone genes are expressed primarily during the S phase of the cell cycle and code for the bulk of cellular histones. Histone variants are usually present as single-copy genes that are not restricted in their expression to S phase, contain introns and are often polyadenylated (Old & Woodland 1984). Some variants have significant differences in primary sequence and distinct biophysical characteristics that are thought to alter the properties of nucleosomes. Others localize to specific regions of the genome. Some variants can exchange with pre-existing major histones during development and differentiation, referred to as replacement histones (Kamakaka & Biggins 2005). These variants can become the predominant species in differentiated cells (Pina & Suau 1987, Wunsch et al. 1991). Histone variants may have specialized functions in regulating chromatin dynamics.

The H2A histone family has the highest sequence divergence and largest number of variants. H2A.Z and H2A.XH2A are considered 'universal variants', found in almost all organisms (Talbert & Henikoff 2010). Variants differ mostly in the C-terminus, including the docking domain, implicated in interactions with the (H3-H4)x2 tetramer within the nucleosome, and in the L1 loop, which is the interaction interface of H2A-H2B dimers (Bonisch & Hake 2012). Canonical H2A proteins are expressed almost exclusively during S-phase. There are several nearly identical variants (Marzluff et al. 2002). No functional specialization of these canonical H2A isoforms has been demonstrated (Bonisch & Hake 2012). Reversible histone modifications such as acetylation and methylation regulate transcription from genomic DNA, defining the 'readability' of genes in specific tissues (Kouzarides 2007, Marmorstein & Trievel 2009, Butler et al. 2012).

N.B. The coordinates of post-translational modifications represented here follow Reactome standardized naming, which includes the UniProt standard practice whereby coordinates refer to the translated protein before any further processing. Histone literature typically refers to coordinates of the protein after the initiating methionine has been removed; therefore the coordinates of post-translated histone residues described here are frequently +1 when compared with the literature. For more information on Reactome's standards for naming pathway events, the molecules that participate in them and representation of post-translational modifications, please refer to Naming Conventions on the Reactome Wiki or Jupe et al. 2014.

References

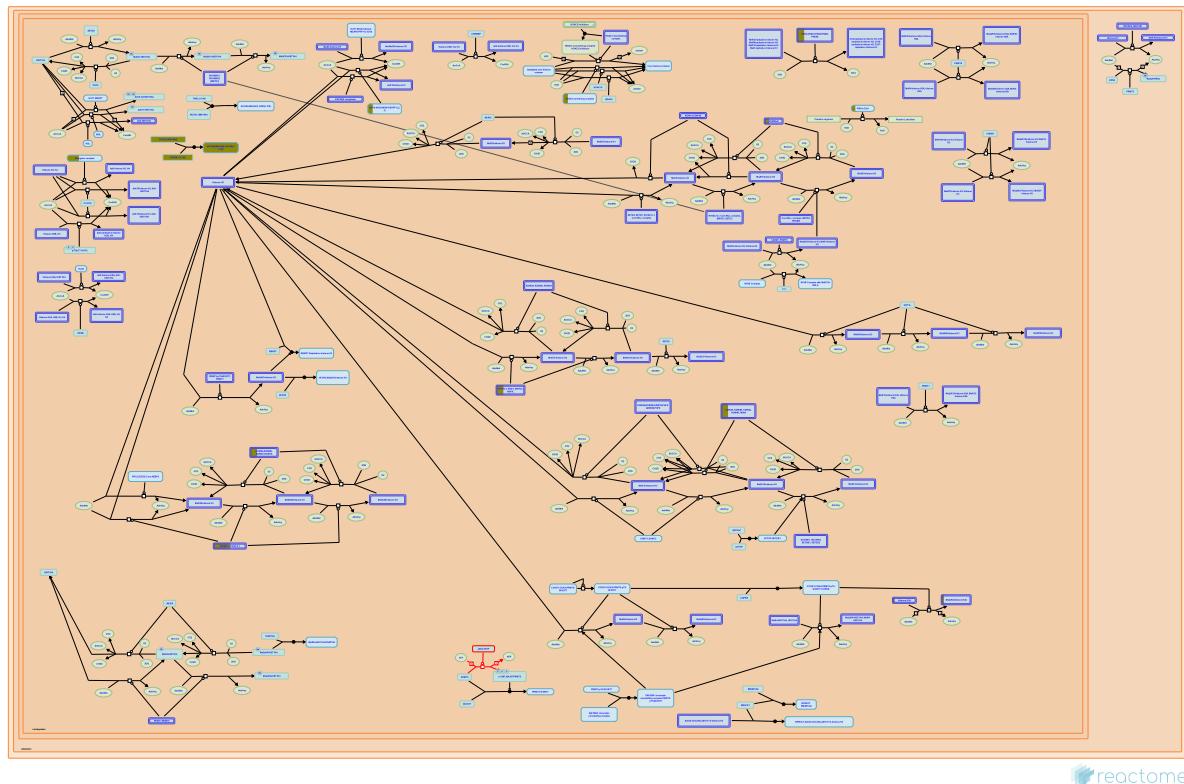
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2013-04-04	Created	Jupe S
2013-11-18	Edited	Jupe S
2013-11-18	Reviewed	Karagiannis T
2021-09-10	Modified	Weiser JD

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

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10499	Q15596	23081	Q9H3R0	26610	Q96EB1
2894	Q9ULC6	55250	Q6IA86	57634	Q96L91
5927	P29375	7403	O15550	7468	O96028
7994	Q92794	83696	P0C0S5	8850	Q92831
9611	O75376				

18. Chromatin organization (R-HSA-4839726)



Cellular compartments: nucleoplasm.

Chromatin organization refers to the composition and conformation of complexes between DNA, protein and RNA. It is determined by processes that result in the specification, formation or maintenance of the physical structure of eukaryotic chromatin. These processes include histone modification, DNA modification, and transcription. The modifications are bound by specific proteins that alter the conformation of chromatin.

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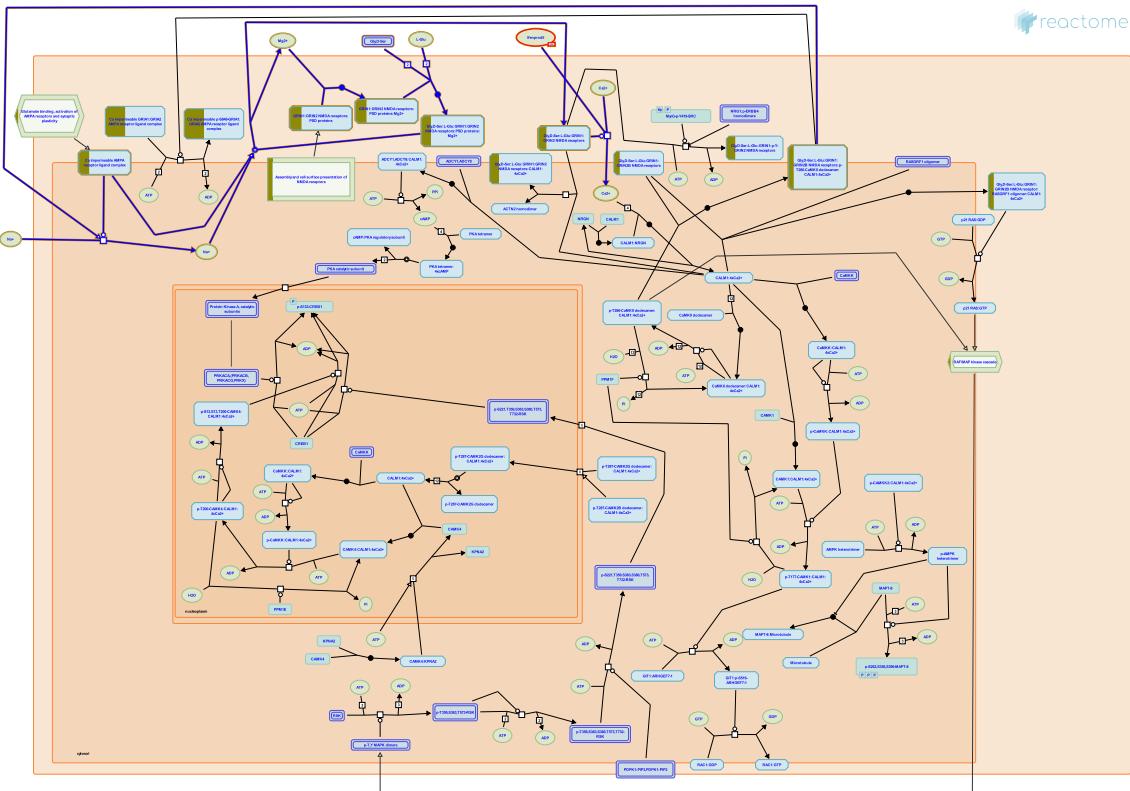
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Date	Action	Author
2013-11-02	Edited	May B
2013-11-02	Authored	May B
2013-11-02	Created	May B
2013-11-18	Reviewed	Karagiannis T
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
10499	Q15596	23081	Q9H3R0	26610	Q96EB1
2894	Q9ULC6	55250	Q6IA86	57634	Q96L91
5927	P29375	7403	O15550	7468	O96028
7994	Q92794	83696	P0C0S5	8850	Q92831
9611	O75376				

19. Unblocking of NMDA receptors, glutamate binding and activation (R-HSA-438066)



Cellular compartments: plasma membrane.

At resting membrane potential, the NMDA receptor ion channel is blocked by extracellular Mg²⁺ ions and is unable to mediate ion permeation upon binding of ligands (glutamate, glycine, D-serine, NMDA). The voltage block is removed upon depolarization of the post-synaptic cell membrane and Mg²⁺ is expelled from the NMDA receptor pore (channel), resulting in activated ligand-bound NMDA receptors. The depolarization of the membrane may happen in response to activation of Ca²⁺ impermeable AMPA receptors, which facilitates Na⁺ influx, contributing to the unblocking of NMDA receptors. For review, please refer to Traynelis et al. 2010, Paoletti et al. 2013, and Iacobucci and Popescu 2017.

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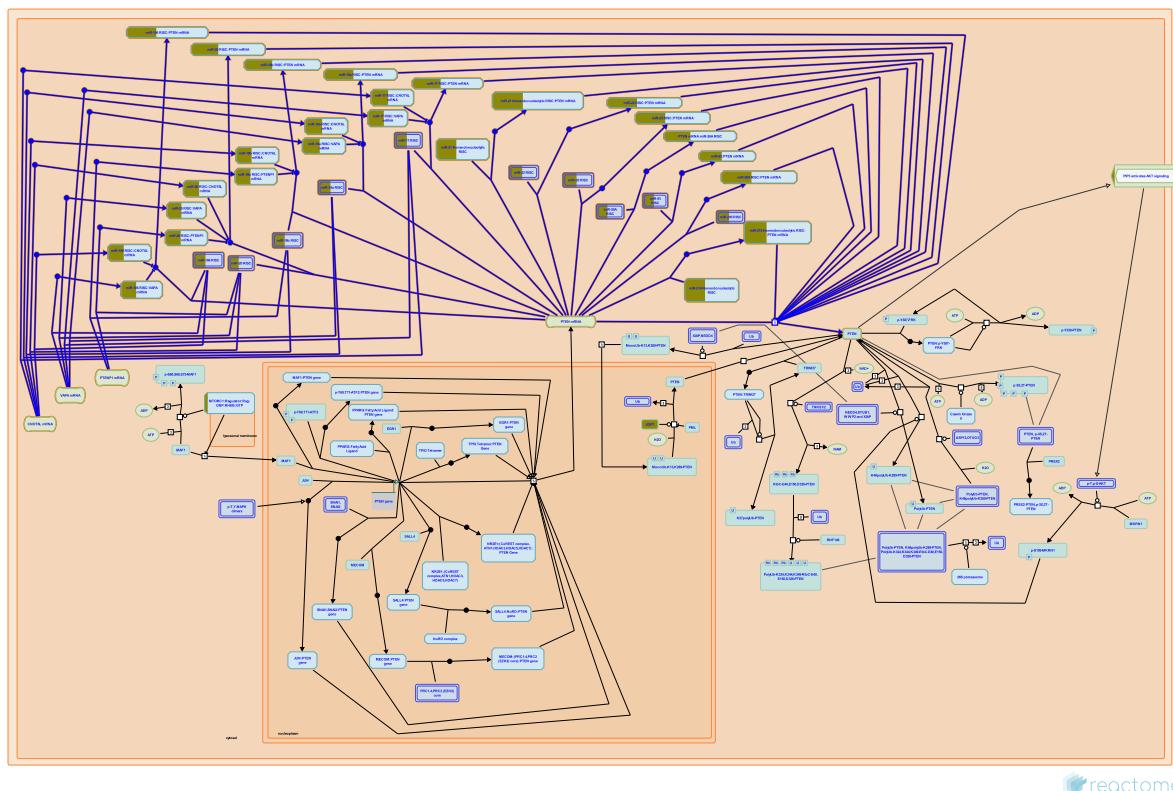
Date	Action	Author
2009-09-23	Created	Mahajan SS

Date	Action	Author
2009-10-29	Authored	Mahajan SS
2009-11-18	Reviewed	Tukey D
2009-11-19	Edited	Gillespie ME
2018-07-31	Edited	Orlic-Milacic M
2018-10-11	Revised	Orlic-Milacic M
2018-11-02	Reviewed	Hansen KB, Yi F
2018-11-07	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
1740	Q15700	2890	P42261
2902	Q05586	2903	Q12879

20. Regulation of PTEN mRNA translation (R-HSA-8943723)



reactome

MicroRNAs miR-17, miR-19a, miR-19b, miR-20a, miR-20b, miR-21, miR-22, miR-25, miR-26A1, miR-26A2, miR-93, miR-106a, miR-106b, miR-205, and miR-214 bind PTEN mRNA and inhibit its translation into protein. These microRNAs are altered in cancer and can account for changes in PTEN levels. There is evidence that PTEN mRNA translation is also inhibited by other microRNAs, such as miR-302 and miR-26B, and these microRNAs will be annotated when additional experimental details become available (Meng et al. 2007, Xiao et al. 2008, Yang et al. 2008, Huse et al. 2009, Kim et al. 2010, Poliseno, Salmena, Riccardi et al. 2010, Zhang et al. 2010, Tay et al. 2011, Qu et al. 2012, Cai et al. 2013). In addition, coding and non coding RNAs can prevent microRNAs from binding to PTEN mRNA. These RNAs are termed competing endogenous RNAs or ceRNAs. Transcripts of the pseudogene PTENP1 and mRNAs transcribed from SERINC1, VAPA and CNOT6L genes exhibit this activity (Poliseno, Salmena, Zhang et al. 2010, Tay et al. 2011, Tay et al. 2014).

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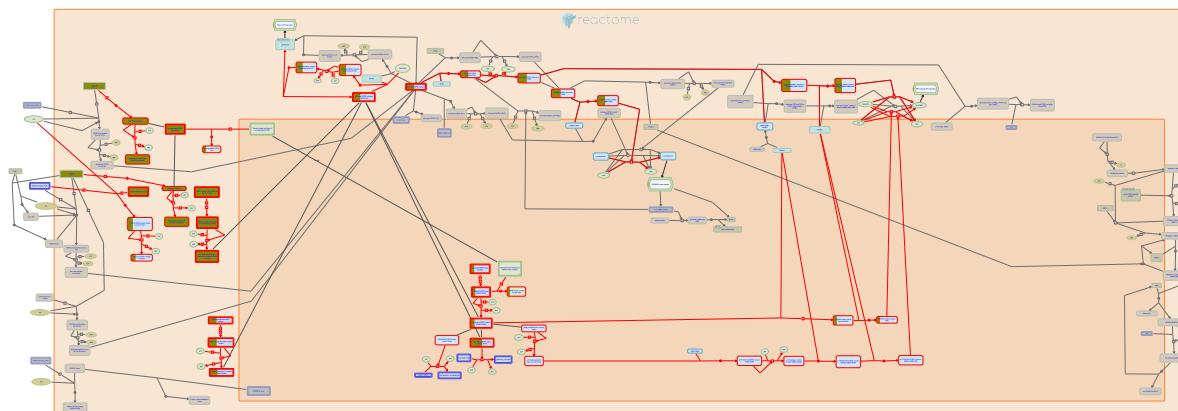
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2016-09-30	Reviewed	Kriplani N, Leslie N
2016-10-28	Authored	Orlic-Milacic M
2016-10-28	Created	Orlic-Milacic M
2017-05-09	Edited	Orlic-Milacic M
2017-05-12	Modified	Orlic-Milacic M

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

Input	UniProt Id	Input	UniProt Id
192670	Q9HCK5	23112	Q9UPQ9
26523	Q9UL18	27161	Q9UKV8

21. Signaling by FGFR1 in disease (R-HSA-5655302)



Diseases: cancer, bone development disease.

The FGFR1 gene has been shown to be subject to activating mutations, chromosomal rearrangements and gene amplification leading to a variety of proliferative and developmental disorders depending on whether these events occur in the germline or arise somatically (reviewed in Webster and Donoghue, 1997; Burke, 1998; Cunningham, 2007; Wesche, 2011; Greulich and Pollock, 2011).

Activating mutation P252R in FGFR1 is associated with the development of Pfeiffer syndrome, characterized by craniosynostosis (premature fusion of several sutures in the skull) and broadened thumbs and toes (Muenke, 1994; reviewed in Cunningham, 2007). This residue falls in a highly conserved Pro-Ser dipeptide between the second and third Ig domains of the extracellular region of the receptor. The mutation is thought to increase the number of hydrogen bonds formed with the ligand and thereby increase ligand-binding affinity (Ibrahim, 2004a). Unlike other FGF receptors, few activating point mutations in the FGFR1 coding sequence have been identified in cancer. Point mutations in the Ig II-III linker analogous to the P252R Pfeiffer syndrome mutation have been identified in lung cancer and melanoma (Ruhe, 2007; Davies, 2005), and two kinase-domain mutations in FGFR1 have been identified in glioblastoma (Rand, 2005, Network TCGA, 2008).

In contrast, FGFR1 is a target of chromosomal rearrangements in a number of cancers. FGFR1 has been shown to be recurrently translocated in the 8p11 myeloproliferative syndrome (EMS), a pre-leukemic condition also known as stem cell leukemia/lymphoma (SCLL) that rapidly progresses to leukemia. This translocation fuses the kinase domain of FGFR1 with the dimerization domain of one of 10 identified fusion partners, resulting in the constitutive dimerization and activation of the kinase (reviewed in Jackson, 2010).

Amplification of the FGFR1 gene has been implicated as an oncogenic factor in a range of cancers, including breast, ovarian, bladder, lung, oral squamous carcinomas, and rhabdomyosarcoma (reviewed in Turner and Grose, 2010; Wesche, 2011; Greulich and Pollock, 2011), although there are other candidate genes in the amplified region and the definitive role of FGFR1 has not been fully established.

More recently, FGFR1 fusion proteins have been identified in a number of cancers; these are thought to undergo constitutive ligand-independent dimerization and activation based on dimerization motifs found in the fusion partners (reviewed in Parker, 2014).

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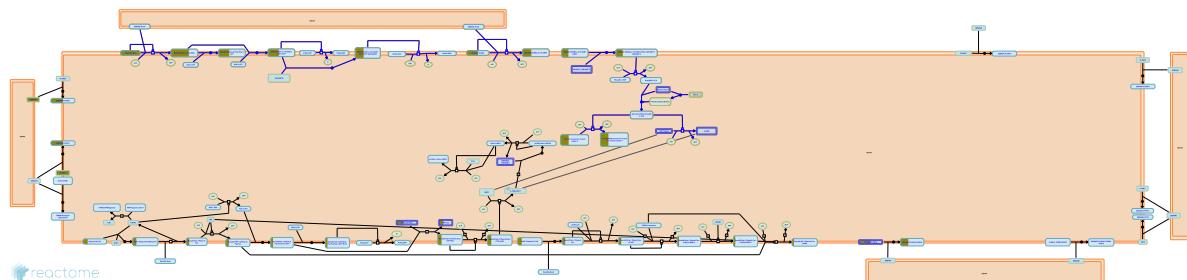
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2012-05-15	Reviewed	Ezzat S
2014-11-20	Authored	Rothfels K
2014-12-05	Edited	Rothfels K
2014-12-05	Created	Rothfels K
2016-01-22	Modified	Rothfels K

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
1523	P39880	2260	P11362, P11362-1, P11362-19	7750	Q9UBW7

22. Sema4D in semaphorin signaling (R-HSA-400685)



Semaphorin 4D (Sema 4D/CD100) is an axon guidance molecule with two disulfide-linked 150-kDa subunits. SEMA4D is structurally defined by a conserved 500-amino acid extracellular domain with 16 cysteines (sema domain) and also an Ig-like domain C-terminal to the sema domain. Sema4D is expressed on the cell surface as a homodimer; cysteine 679 within the sema domain is required for this dimerization.

The main receptors for Sema4D are plexin-B1 and CD72. The activation of plexins by semaphorins initiates a variety of signaling processes that involve several small GTPases of the Ras and Rho families. Sema4D-Plexin-B1 interaction appears to mediate different and sometimes opposite effects depending on the cellular context. Plexin-B1 activation inhibits integrin-mediated cell attachment and cell migration through the activation of the R-RasGAP activity inherent to plexin-B1 or through the inhibition of RhoA. However, activation of plexin-B1 by Sema4D stimulates the migration of endothelial cells by mediating the activation of RhoA.

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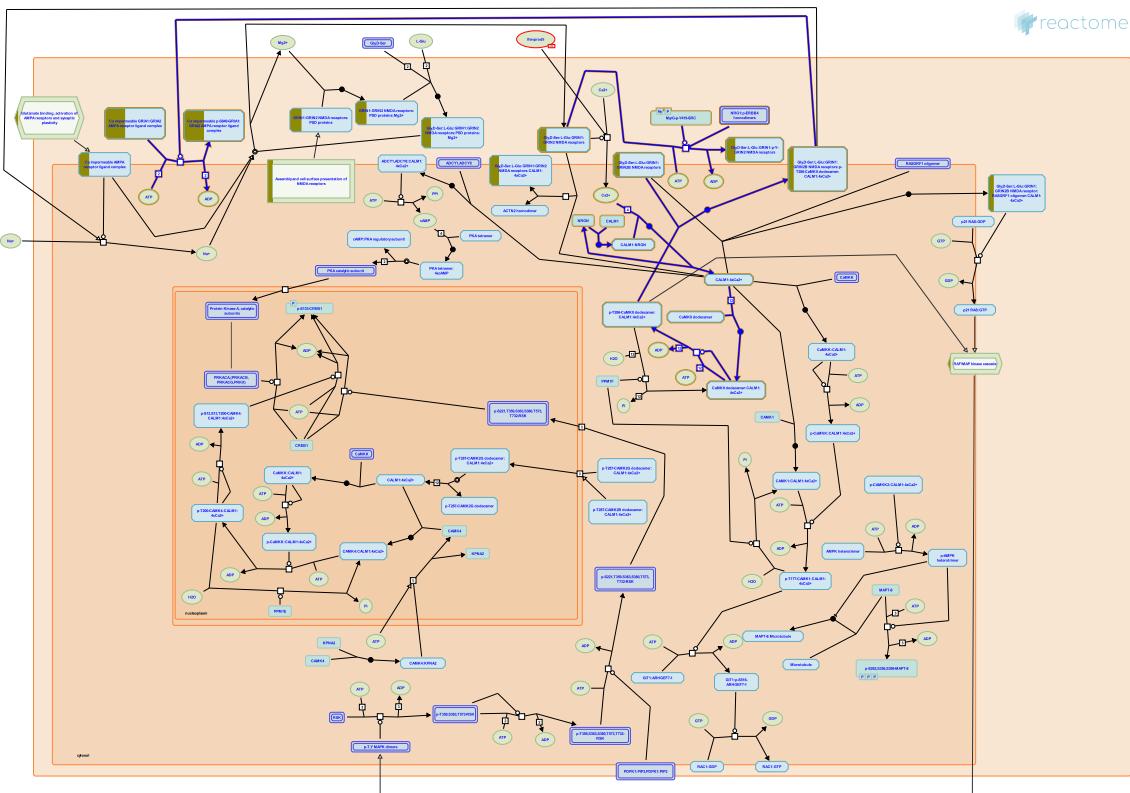
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2009-03-23	Edited	Garapati P V
2009-03-23	Authored	Garapati P V
2009-03-24	Created	Garapati P V
2009-09-02	Reviewed	Kumanogoh A, Kikutani H
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
4233	P08581	4627	P35579
4628	P35580	5364	O43157

23. Long-term potentiation (R-HSA-9620244)



In long-term potentiation (LTP), involved in learning and memory, a brief period of synaptic activity induces a lasting increase in the strength of the synapse. LTP is initiated by NMDA receptor-mediated activation of calcium/calmodulin-dependent protein kinase II (CaMKII), followed by binding of CaMKII to the NMDA receptor and CaMKII-mediated phosphorylation of AMPA receptor sub-units (reviewed by Lisman et al. 2012 and Lüscher and Malenka 2012).

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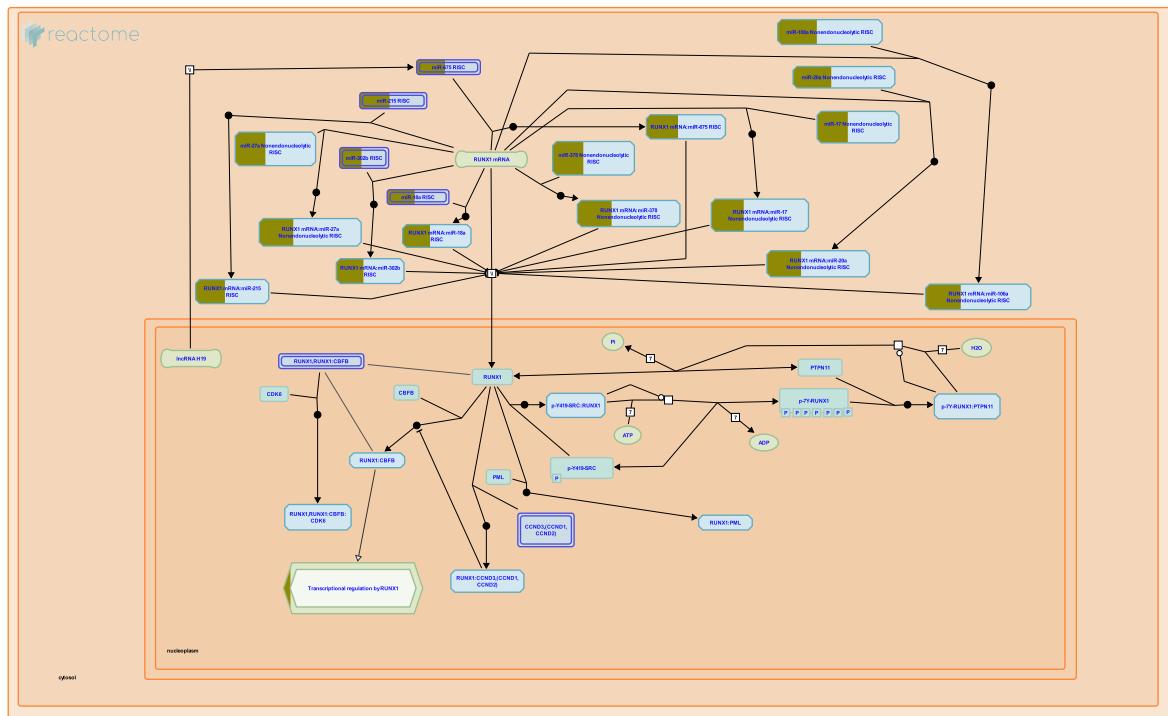
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2018-10-11	Authored	Orlic-Milacic M
2018-11-02	Reviewed	Hansen KB, Yi F
2018-11-07	Edited	Orlic-Milacic M
2021-09-20	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
1740	Q15700	2890	P42261
2902	Q05586	2903	Q12879

24. Regulation of RUNX1 Expression and Activity (R-HSA-8934593)



At the level of transcription, expression of the RUNX1 transcription factor is regulated by two alternative promoters: a distal promoter, P1, and a proximal promoter, P2. P1 is more than 7 kb upstream of P2 (Ghozi et al. 1996). In mice, the Runx1 gene is preferentially transcribed from the proximal P2 promoter during generation of hematopoietic cells from hemogenic endothelium. In fully committed hematopoietic progenitors, the Runx1 gene is preferentially transcribed from the distal P1 promoter (Sroczynska et al. 2009, Bee et al. 2010). In human T cells, RUNX1 is preferentially transcribed from P1 throughout development, while developing natural killer cells transcribe RUNX1 predominantly from P2. Developing B cells transcribe low levels of RUNX1 from both promoters (Telfer and Rothenberg 2001).

RUNX1 mRNAs transcribed from alternative promoters differ in their 5'UTRs and splicing isoforms of RUNX1 have also been described. The function of alternative splice isoforms and alternative 5'UTRs has not been fully elucidated (Challen and Goodell 2010, Komano et al. 2014).

During zebrafish hematopoiesis, RUNX1 expression increases in response to NOTCH signaling, but direct transcriptional regulation of RUNX1 by NOTCH has not been demonstrated (Burns et al. 2005). RUNX1 transcription also increases in response to WNT signaling. Both TCF7 and TCF4 bind the RUNX1 promoter (Wu et al. 2012, Hoverter et al. 2012), and RUNX1 transcription driven by the TCF binding element (TBE) in response to WNT3A treatment is inhibited by the dominant-negative mutant of TCF4 (Medina et al. 2016). In developing mouse ovary, Runx1 expression is positively regulated by Wnt4 signaling (Naillat et al. 2015).

Studies in mouse hematopoietic stem and progenitor cells imply that RUNX1 may be a direct transcriptional target of HOXB4 (Oshima et al. 2011).

Conserved cis-regulatory elements were recently identified in intron 5 of RUNX1. The RUNX1 breakpoints observed in acute myeloid leukemia (AML) with translocation (8;21), which result in expression of a fusion RUNX1-ETO protein, cluster in intron 5, in proximity to these not yet fully characterized cis regulatory elements (Rebolledo-Jaramillo et al. 2014).

At the level of translation, RUNX1 expression is regulated by various microRNAs which bind to the 3'UTR of RUNX1 mRNA and inhibit its translation through endonucleolytic and/or nonendonucleolytic mechanisms. MicroRNAs that target RUNX1 include miR-378 (Browne et al. 2016), miR-302b (Ge et al. 2014), miR-18a (Miao et al. 2015), miR-675 (Zhuang et al. 2014), miR-27a (Ben-Ami et al. 2009), miR-17, miR-20a, miR106 (Fontana et al. 2007) and miR-215 (Li et al. 2016).

At the posttranslational level, RUNX1 activity is regulated by postranslational modifications and binding to co-factors. SRC family kinases phosphorylate RUNX1 on multiple tyrosine residues in the negative regulatory domain, involved in autoinhibition of RUNX1. RUNX1 tyrosine phosphorylation correlates with reduced binding of RUNX1 to GATA1 and increased binding of RUNX1 to the SWI/SNF complex, leading to inhibition of RUNX1-mediated differentiation of T-cells and megakaryocytes. SHP2 (PTPN11) tyrosine phosphatase binds to RUNX1 and dephosphorylates it (Huang et al. 2012).

Formation of the complex with CBFB is necessary for the transcriptional activity of RUNX1 (Wang et al. 1996). Binding of CCND3 and probably other two cyclin D family members, CCND1 and CCND2, to RUNX1 inhibits its association with CBFB (Peterson et al. 2005), while binding to CDK6 interferes with binding of RUNX1 to DNA without affecting formation of the RUNX1:CBFB complex. Binding of RUNX1 to PML plays a role in subnuclear targeting of RUNX1 (Nguyen et al. 2005).

RUNX1 activity and protein levels vary during the cell cycle. RUNX1 protein levels increase from G1 to S and from S to G2 phases, with no increase in RUNX1 mRNA levels. CDK1-mediated phosphorylation of RUNX1 at the G2/M transition is implicated in reduction of RUNX1 transactivation potency and may promote RUNX1 protein degradation by the anaphase promoting complex (reviewed by Friedman 2009).

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Edit history

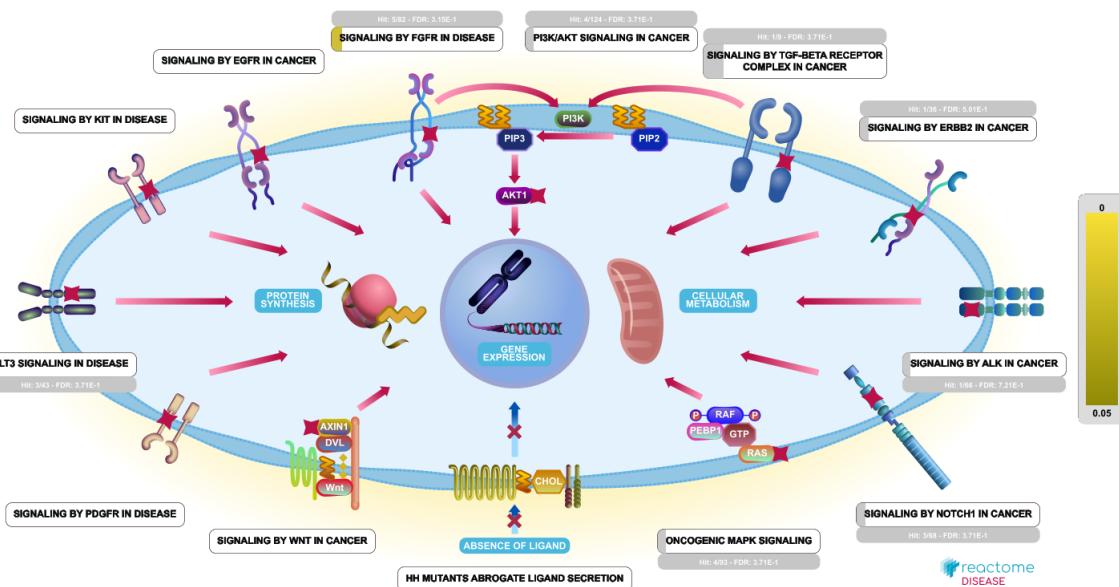
Date	Action	Author
2016-08-11	Created	Orlic-Milacic M
2016-09-14	Authored	Orlic-Milacic M
2016-12-20	Reviewed	Ito Y, Chuang LS

Date	Action	Author
2017-05-12	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
192670	Q9HCK5	23112	Q9UPQ9
26523	Q9UL18	27161	Q9UKV8

25. Diseases of signal transduction by growth factor receptors and second messengers (R-HSA-5663202)



Signaling processes are central to human physiology (e.g., Pires-da Silva & Sommer 2003), and their disruption by either germ-line and somatic mutation can lead to serious disease. Here, the molecular consequences of mutations affecting visual signal transduction and signaling by diverse growth factors are annotated.

References

Pires-daSilva A & Sommer RJ (2003). The evolution of signalling pathways in animal development. Nat. Rev. Genet., 4, 39-49. [View](#)

Edit history

Date	Action	Author
2015-01-16	Created	D'Eustachio P
2021-03-29	Modified	Rothfels K

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
10142	Q99996	1523	P39880	2109	P42345
2200	Q07817	2260	P11362, P11362-1, P11362-19	22866	Q8WXI2
23236	P42345	2475	P42345	3690	P05106
4089	Q13485	4233	P08581	4627	P35579
51107	Q96BI3	5245	P35232	55914	Q96RT1
6711	Q01082	7750	Q9UBW7	8850	Q92831
9611	O75376				

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.

172 of the submitted entities were found, mapping to 228 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
100	P00813	10055	Q9UBE0	1012	Q05940
10142	Q99996	10236	O43390	10243	Q9NQX3
10499	Q15596	10518	O75838	10575	P50991
109	O60266	11198	Q9Y5B9	1139	P36544
116986	Q99490	123169	Q8WVC0	1268	P21554
144165	Q96MT3	1501	P53778	1523	O75582
152330	Q8IWV2	161725	Q8TE49	1630	P43146
1740	Q15700	1747	P16066	192670	Q9HCK5
2109	P42345	2200	Q07817	2239	P07358
2260	P11362-1	22866	Q8WXI2	22871	Q8N2Q7
22981	Q9Y2I6	22986	P42568	23013	Q96T58
23019	A5YKK6	23081	Q9H3R0	23112	Q9UPQ9
23191	Q7L576	23211	P07237	23236	Q9NQ66
23259	O94830	23309	O75182	23332	Q7Z460
2475	P42345	2483	O75881	2567	Q99928
25865	Q9BZL6	26047	P55087	26050	O94991
26057	Q5D862	26290	Q9NY28	26512	Q9UL03
26523	Q9UL18	26610	Q96EB1	270	Q9NS75
27071	Q9UN19	27131	P00973	27161	Q9UKV8
27185	Q96BT3	27255	Q9UQ52	275	P21453
2890	P42261	2894	Q9ULC6	2898	Q13002
2901	Q16478	2902	Q05586	2903	Q12879
29998	P46098	301	P04083	3150	Q5EBL8
3184	P29475	3185	P35228	3190	P12318
322	O43614	3382	Q08209	339122	Q86YS6
3608	Q12905	3690	P05106	3720	Q92833
3766	P78508	3785	O43526, P61764	3790	Q9BQ31
3912	P07942	4035	Q07954	4089	Q13485
4233	P08581	43	P22303	4308	Q7Z4N2
4627	P35579	4628	P35580	4644	Q9Y4I1
4650	Q13459	493	P23634	4983	O60890
5021	P30559	5026	Q93086	5062	Q13177
5071	O60260	50944	Q9Y566	51107	Q96BI3
5119	Q9HD42	51741	Q9NZC7	5245	P35232
5364	O43157	53942	O94779	5444	P27169
547	Q92953	54715	Q9NWB1	54790	Q6N021
552	Q9NSA2	55217	Q9NVH6	55250	Q6IA86
55568	Q86SR1	5579	P05771	55914	Q96RT1
5625	O43272	57148	Q86X10	57194	O60312
57468	Q9H2X9	57520	Q9P2P5	57578	Q9P2D8
57580	Q8TCU6	57634	Q96L91	5862	P61019

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
59269	Q5T1R4	5927	P29375	6092	Q9HCK4
6305	O95248	6335	Q15858	6418	Q01105
6531	Q01959	6711	Q01082	6878	P49848
7014	Q15554	7225	Q9Y210	7403	O15550
7468	O96028	7750	Q9UBW7	776	Q01668
783	Q08289	7874	Q93009	7994	Q92794
8128	Q92186	8140	Q01650	81704	Q8NF50
83696	P0C0S5	8404	Q14515	84623	Q8IZU9
84889	Q8WY07	84952	P33527	85015	Q70EL2
85445	O15033	8850	Q92831	8864	O15055
8912	O95180	8974	O15460	900	P82251
9037	Q13591	91584	O60486, Q9HCM2	91752	Q15173
9229	O14490	9295	Q05519	93594	O43752
95681	Q9BYV8	9578	Q9Y5S2	9611	O75376
9662	Q66GS9	9690	Q15386	9820	Q14999
9891	O60285	9928	Q15058	9958	Q9Y4E8
Input	ChEBI Id	Input	ChEBI Id	Input	ChEBI Id
26523	26523	57634	57634	57705	57705

7. Identifiers not found

These 47 identifiers were not found neither mapped to any entity in Reactome.

100128977	100873065	10237	10771	114902	117583	119772	124565
134492	134957	140733	149628	166336	221092	22982	23167
23245	254048	259266	340533	4010	406928	51366	51533
54439	54862	54870	56946	57178	57466	57628	57661
57691	6473	64901	7429	79026	79893	79937	80315
83992	8562	8853	89797	9044	9344	9603	