reactome

Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 88 on 11/04/2024. The web link to these results is:

https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyNDA0MTExNTQ0MTBfMzYyOA%3D%3D

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

Table of Contents

1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for Homo sapiens are available for 14 non-human species including mouse, rat, chicken, puffer fish, worm, fly and yeast. 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:

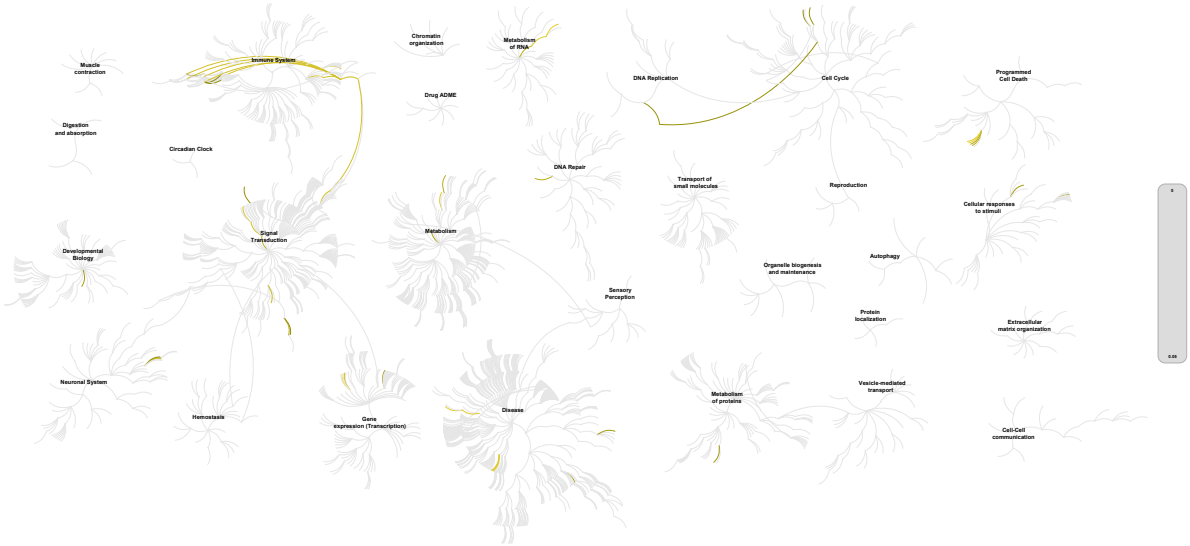
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, … D'Eustachio P (2016). The reactome pathway knowledgebase. Nucleic Acids Research, 44(D1), D481–D487. https://doi.org/10.1093/nar/gkv1351.

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.
- 7 out of 8 identifiers in the sample were found in Reactome, where 426 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent.
- IntAct interactors were included to increase the analysis background. This greatly increases the size of Reactome pathways, which maximises the chances of matching your submitted identifiers to the expanded pathway, but will include interactors that have not undergone manual curation by Reactome and may include interactors that have no biological significance, or unexplained relevance.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyNDA0MTExNTQ0MTBfMzYyOA%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
MECP2 regulates transcription factors	2 / 44	0.002	4.32e-04	0.166	2 / 8	5.37e-04
Defective Mismatch Repair Associated With MSH2	1 / 8	3.48e-04	0.006	0.166	1 / 2	1.34e-04
Activation of NOXA and translocation to mitochondria	1 / 11	4.78e-04	0.008	0.166	2 / 5	3.36e-04
Formation of editosomes by ADAR proteins	1 / 13	5.65e-04	0.009	0.166	1 / 4	2.69e-04
Activation of PUMA and translocation to mitochondria	1 / 15	6.52e-04	0.01	0.166	2 / 5	3.36e-04
mRNA Editing: A to I Conversion	1 / 15	6.52e-04	0.01	0.166	1 / 6	4.03e-04
MAPK targets/ Nuclear events mediated by MAP kinases	3 / 228	0.01	0.011	0.166	9 / 16	0.001
Defective binding of RB1 mutants to E2F1,(E2F2, E2F3)	1 / 17	7.39e-04	0.012	0.166	1 / 1	6.72e-05
Aberrant regulation of mitotic G1/S transition in cancer due to RB1 defects	1 / 17	7.39e-04	0.012	0.166	1 / 2	1.34e-04
CREB1 phosphorylation through the activation of Adenylate Cyclase	1 / 17	7.39e-04	0.012	0.166	1 / 6	4.03e-04
Pre-NOTCH Transcription and Translation	3 / 239	0.01	0.012	0.166	3 / 28	0.002
Defective Mismatch Repair Associated With MSH6	1 / 18	7.83e-04	0.012	0.166	1 / 1	6.72e-05
PDH complex synthesizes acetyl-CoA from PYR	1 / 19	8.26e-04	0.013	0.166	3 / 3	2.02e-04
Defective Mismatch Repair Associated With MSH3	1 / 19	8.26e-04	0.013	0.166	1 / 1	6.72e-05
CREB phosphorylation	3 / 24	0.001	0.017	0.166	4 / 4	2.69e-04
Interleukin-38 signaling	1 / 24	0.001	0.017	0.166	1 / 5	3.36e-04
MAP kinase activation	3 / 290	0.013	0.017	0.166	9 / 32	0.002
Interleukin-17 signaling	3 / 300	0.013	0.018	0.166	9 / 35	0.002
MECP2 regulates transcription of neuronal ligands	1 / 27	0.001	0.019	0.166	2 / 8	5.37e-04
Pre-NOTCH Expression and Processing	3 / 307	0.013	0.019	0.166	3 / 38	0.003
AKT phosphorylates targets in the nucleus	1 / 31	0.001	0.021	0.166	1 / 4	2.69e-04

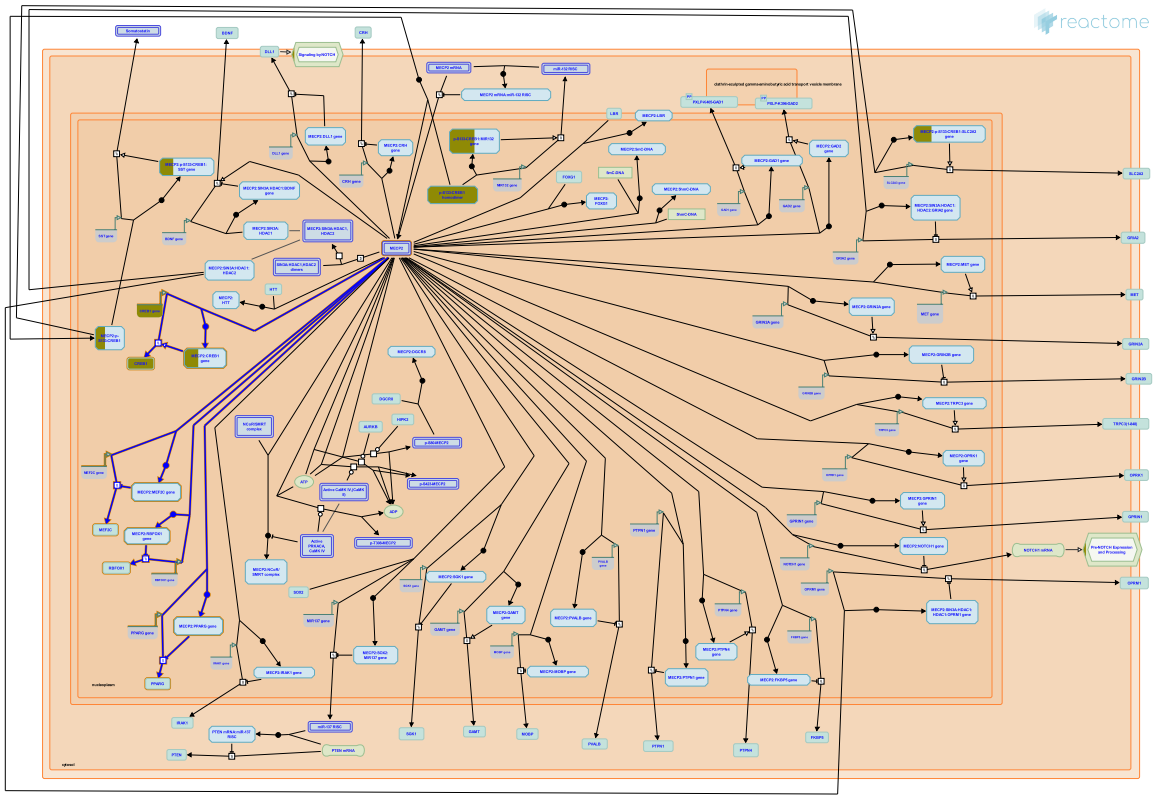
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
PKA-mediated phosphorylation of CREB	1 / 37	0.002	0.025	0.166	2 / 7	4.70e-04
CREB1 phosphorylation through NMDA receptor-mediated activation of RAS signaling	1 / 39	0.002	0.027	0.166	1 / 7	4.70e-04
Activation of BIM and translocation to mitochondria	1 / 42	0.002	0.029	0.166	1 / 2	1.34e-04
Mismatch repair (MMR) directed by MSH2:MSH3 (MutSbeta)	1 / 42	0.002	0.029	0.166	1 / 9	6.05e-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. MECP2 regulates transcription factors (R-HSA-9022707)



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).

References

McKnight RA, Lane RH, Callaway CW, Ogata EM, Albertine KH, Sainz AJ, ... Wang Y (2011). IUGR differentially alters MeCP2 expression and H3K9Me3 of the PPARΒ gene in male and female rat lungs during alveolarization. Birth Defects Res. Part A Clin. Mol. Teratol., 91, 672-81.

Chu DC, Oakley F, Maxwell A, Tsukamoto H, Zhu NL, Mann J & Mann DA (2010). MeCP2 controls an epigenetic pathway that promotes myofibroblast transdifferentiation and fibrosis. Gastroenterology, 138, 705-14, 714.e1-4.

Qin J, Jung SY, Wong ST, Zoghbi HY, Shaw C, Chahrour M & Zhou X (2008). MeCP2, a key contributor to neurological disease, activates and represses transcription. Science, 320, 1224-9.

Edit history

Date	Action	Author
2017-09-25	Created	Orlic-Milacic M
2017-10-02	Authored	Orlic-Milacic M

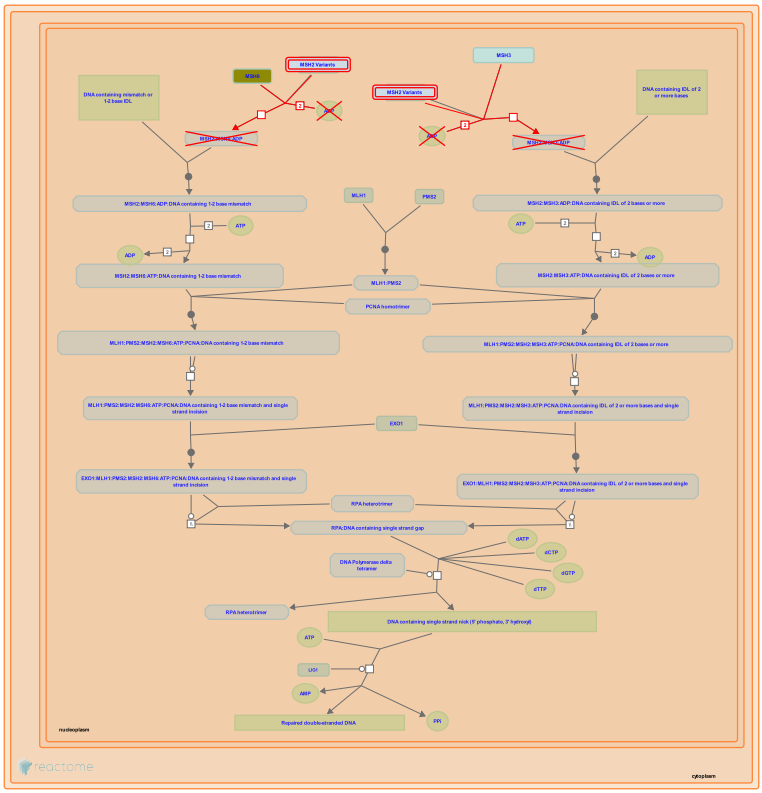
Date	Action	Author
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2023-03-08	Modified	Matthews L

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

Input	UniProt Id
CREB1	P16220-1

Input	Ensembl Id
CREB1	ENSG00000118260

2. Defective Mismatch Repair Associated With MSH2 (R-HSA-5632928)



Cellular compartments: nucleoplasm.

Diseases: cancer.

MSH2 is homologous to the E. coli MutS gene and is involved in DNA mismatch repair (MMR) (Fishel et al., 1994). Heterozygous mutations in the MSH2 gene result in hereditary nonpolyposis colorectal cancer-1. Variants of MSH2 are associated with hereditary nonpolyposis colorectal cancer. Alteration of MSH2 is also involved in Muir-Torre syndrome and mismatch repair cancer syndrome.

References

Dunlop MG, Farrington SM, Mitchell RJ & Campbell H (2002). Mismatch repair genes hMLH1 and hMSH2 and colorectal cancer: a HuGE review. Am. J. Epidemiol., 156, 885-902.

Copeland NG, Kane M, Rao MR, Jenkins NA, Lescoe MK, Kolodner R, ... Fishel R (1993). The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. Cell, 75, 1027-38.

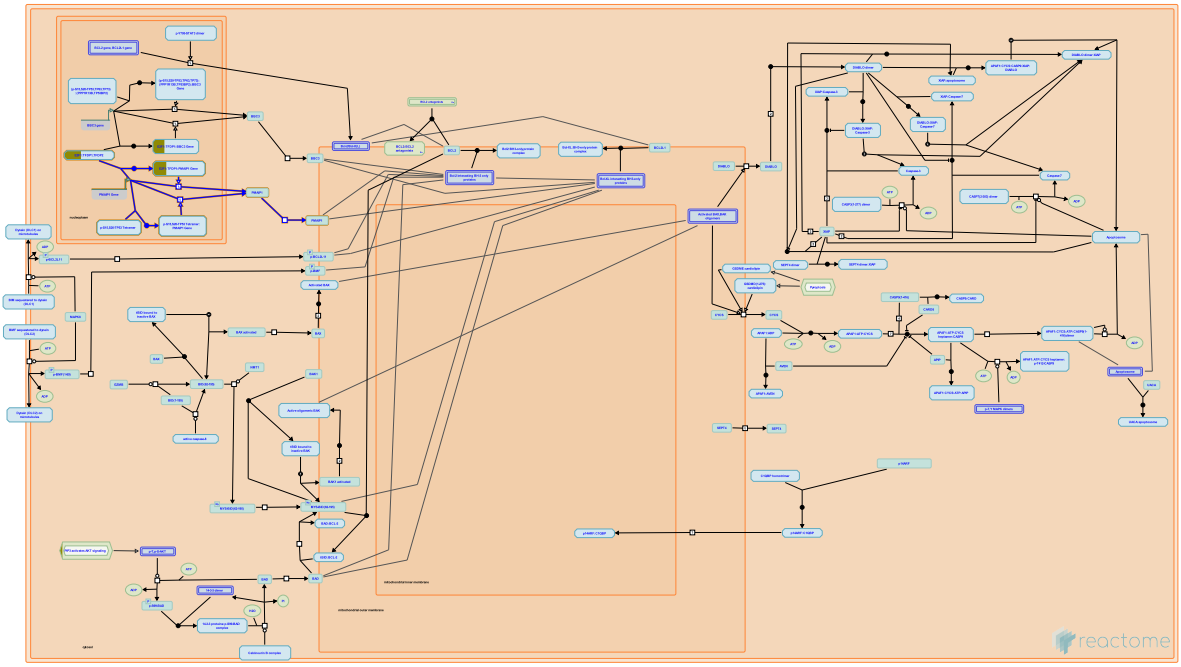
Edit history

Date	Action	Author
2011-11-10	Authored	Gillespie ME
2014-10-29	Created	Gillespie ME
2016-11-01	Reviewed	Arora S
2017-02-27	Edited	Gillespie ME
2023-03-08	Modified	Matthews L

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

Input	UniProt Id
MSH6	P52701

3. Activation of NOXA and translocation to mitochondria (R-HSA-111448)



Cellular compartments: cytosol.

NOXA is transactivated in a p53-dependent manner and by E2F1. Activated NOXA is translocated to mitochondria.

References

Hershko T & Ginsberg D (2004). Up-regulation of Bcl-2 homology 3 (BH3)-only proteins by E2F1 mediates apoptosis. J Biol Chem, 279, 8627-34.

Hanigan CL, Robles AI, Trudel LJ, Hofseth LJ, Li CQ, Wogan GN & Harris CC (2004). Apoptotic signaling pathways induced by nitric oxide in human lymphoblastoid cells expressing wild-type or mutant p53. Cancer Res, 64, 3022-9.

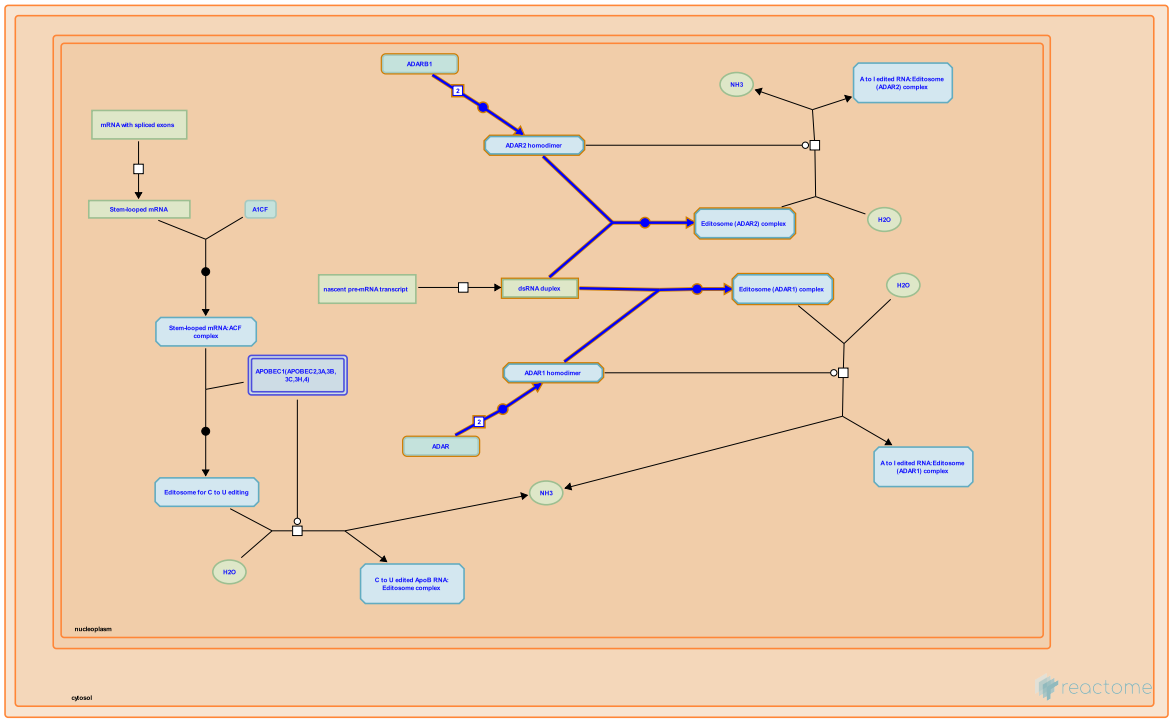
Edit history

Date	Action	Author
2004-08-09	Created	Tsujimoto Y, Hardwick JM

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

Input	UniProt Id
TFDP1	Q14186

4. Formation of editosomes by ADAR proteins (R-HSA-77042)



Cellular compartments: nucleoplasm.

It is still unclear how ADAR 1 and ADAR 2 proteins form the editosomes with the target RNA. Other components of these editosomes for A to I editing are unknown.

References

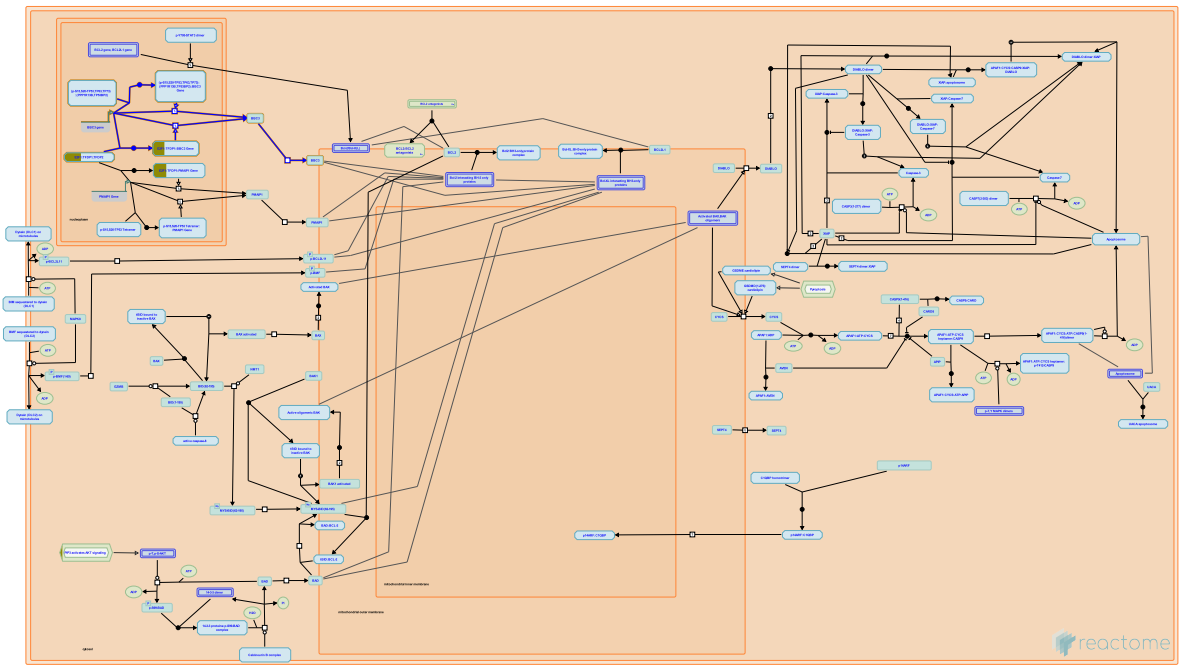
Edit history

Date	Action	Author
2003-12-05	Authored	Gopinathrao G
2003-12-05	Created	Carmichael GG
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JUN	P05412	P78563			

5. Activation of PUMA and translocation to mitochondria (R-HSA-139915)



Cellular compartments: cytosol.

Puma is transactivated in a p53-dependent manner and by E2F1. Activated Puma is translocated to mitochondria.

References

Hershko T & Ginsberg D (2004). Up-regulation of Bcl-2 homology 3 (BH3)-only proteins by E2F1 mediates apoptosis. J Biol Chem, 279, 8627-34.

Nakano K & Vousden KH (2001). PUMA, a novel proapoptotic gene, is induced by p53. Mol Cell, 7, 683-94.

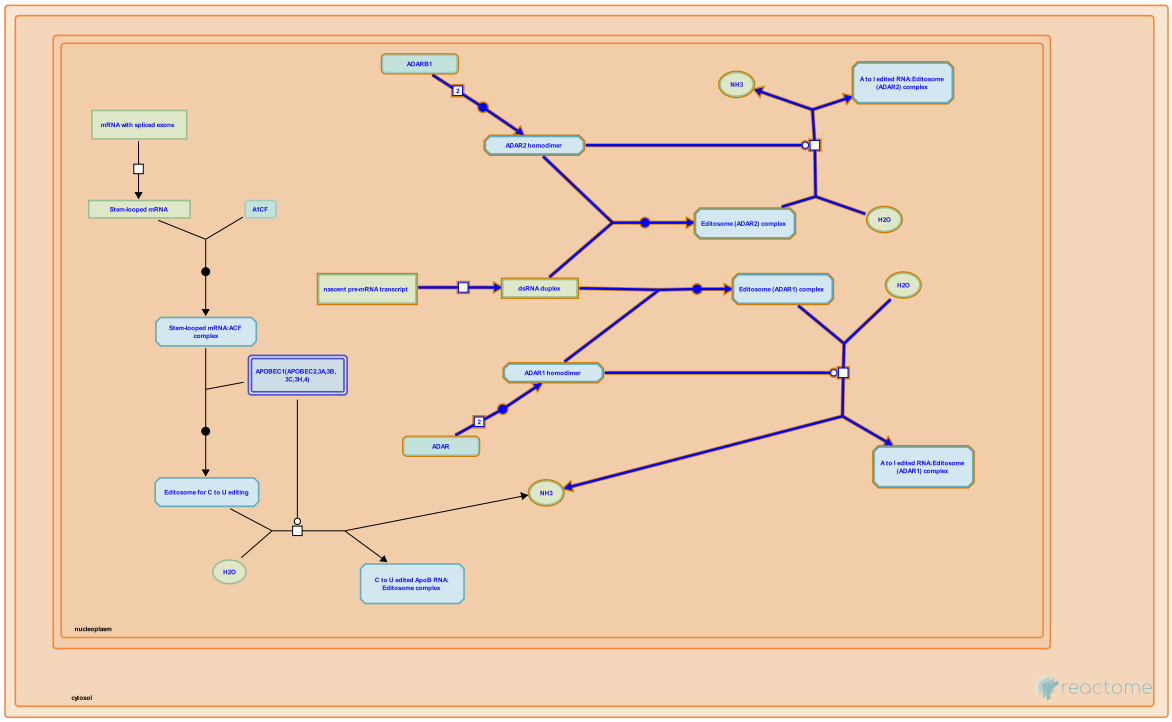
Edit history

Date	Action	Author
2004-08-09	Created	Tsujimoto Y, Hardwick JM

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

Input	UniProt Id
TFDP1	Q14186

6. mRNA Editing: A to I Conversion (R-HSA-75064)



Cellular compartments: nucleoplasm.

In humans the deamination of adenosines to inosines is the most common editing event. It is particularly prevalent in the brain, where it leads to amino acid changes that affect the conductance of several ion channels. Inosines are recognized by the translation machinery as if they were guanosines.

ADARs (Adenosine Deaminases Acting on RNA) modify pre-mRNA, acting as single peptides and recognize structural determinants in the RNA. To date 3 members of this deaminase family are known: ADAR 1, ADAR 2, and ADAR 3 that share a common modular domain structure. ADAR 1 and 2 contain a catalytic deaminase domain, a double-stranded RNA binding domain and exhibit RNA editing activity. ADAR1 activity is found in various mammalian tissues with the highest concentration in brain.

An increasing number of mammalian genes have been found to undergo deamination by ADARs. Deamination by editing in pre-mRNAs encoding subunits of ionotropic glutamate receptors (GluRs) is another well studied example. An editing event at the Q/R site of the GluR2 (GluRB) subunit of AMPA receptors converts a Gln codon CAG to an Arg codon CIG rendering the heteromeric receptor impermeable to Ca 2+ ions. Another example is the editing of 5-HT2C subtype serotonin receptor mRNA resulting in receptor isoforms with reduced G-protein coupling efficiency (reviewed by Gerber and Keller, 2001).

In mice, the editosomes with ADAR proteins require some cis-acting elements like an intronic 'editing-site complementary sequence (ECS)'. Although evolutionarily conserved, the actual role of ECS is not yet elucidated in humans. The editing complex can be generally represented as:

References

Keller W & Gerber AP (2001). RNA editing by base deamination: more enzymes, more targets, new mysteries. Trends Biochem Sci, 26, 376-84.

Pomerantz SC, McCloskey JA, Crain PF, Polson AG & Bass BL (1992). The mechanism of adenosine to inosine conversion by the double-stranded RNA unwinding/modifying activity: a high-performance liquid chromatography-mass spectrometry analysis. Biochemistry, 30, 11507-14.

Bass BL (2002). RNA editing by adenosine deaminases that act on RNA. Annu Rev Biochem, 71, 817-46.

Davidson NO & Blanc V (2003). C-to-U RNA editing: mechanisms leading to genetic diversity. J Biol Chem, 278, 1395-8.

Higuchi M, Herb A, Sprengel R, Maas S, Seeburg PH & Melcher T (1997). RED2, a brain-specific member of the RNA-specific adenosine deaminase family. J Biol Chem, 271, 31795-8.

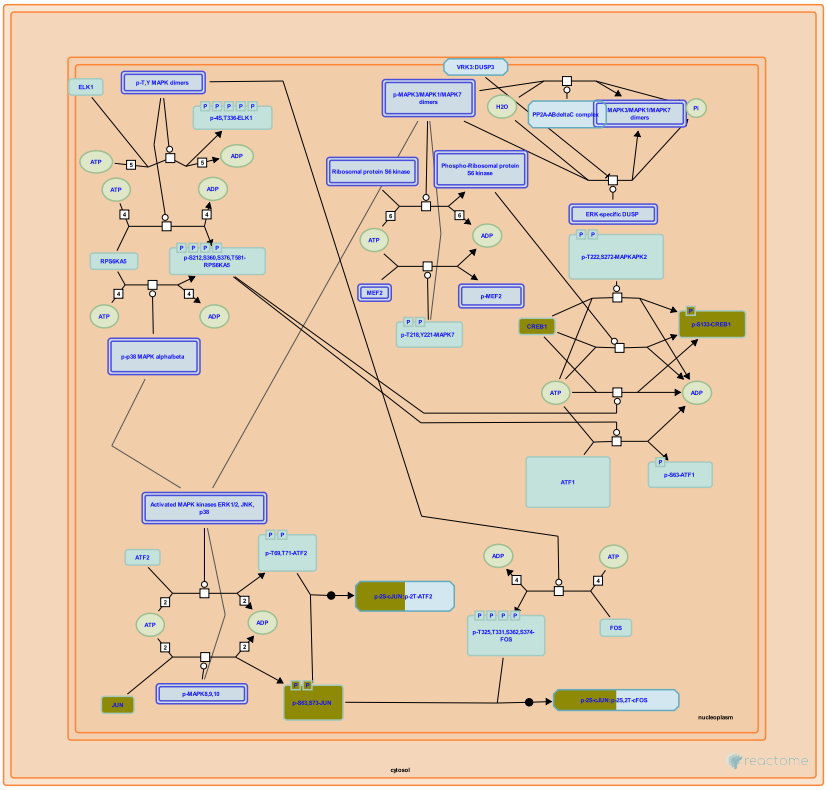
Edit history

Date	Action	Author
2003-08-22	Authored	Carmichael GG
2003-08-22	Created	Carmichael GG
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JUN	P05412	P78563			

7. MAPK targets/ Nuclear events mediated by MAP kinases (R-HSA-450282)



MAPKs are protein kinases that, once activated, phosphorylate their specific cytosolic or nuclear substrates at serine and/or threonine residues. Such phosphorylation events can either positively or negatively regulate substrate, and thus entire signaling cascade activity.

The major cytosolic target of activated ERKs are RSKs (90 kDa Ribosomal protein S6 Kinase). Active RSKs translocates to the nucleus and phosphorylates such factors as c-Fos(on Ser362), SRF (Serum Response Factor) at Ser103, and CREB (Cyclic AMP Response Element-Binding protein) at Ser133. In the nucleus activated ERKs phosphorylate many other targets such as MSKs (Mitogen- and Stress-activated protein kinases), MNK (MAP interacting kinase) and Elk1 (on Serine383 and Serine389). ERK can directly phosphorylate CREB and also AP-1 components c-Jun and c-Fos. Another important target of ERK is NF-KappaB. Recent studies reveals that nuclear pore proteins are direct substrates for ERK (Kosako H et al, 2009). Other ERK nuclear targets include c-Myc, HSF1 (Heat-Shock Factor-1), STAT1/3 (Signal Transducer and Activator of Transcription-1/3), and many more transcription factors.

Activated p38 MAPK is able to phosphorylate a variety of substrates, including transcription factors STAT1, p53, ATF2 (Activating transcription factor 2), MEF2 (Myocyte enhancer factor-2), protein kinases MSK1, MNK, MAPKAPK2/3, death/survival molecules (Bcl2, caspases), and cell cycle control factors (cyclin D1).

JNK, once activated, phosphorylates a range of nuclear substrates, including transcription factors Jun, ATF, Elk1, p53, STAT1/3 and many other factors. JNK has also been shown to directly phosphorylate many nuclear hormone receptors. For example, peroxisome proliferator-activated receptor 1 (PPAR-1) and retinoic acid receptors RXR and RAR are substrates for JNK. Other JNK targets are heterogeneous nuclear ribonucleoprotein K (hnRNP-K) and the Pol I-specific transcription factor TIF-IA, which regulates ribosome synthesis. Other adaptor and scaffold proteins have also been characterized as nonnuclear substrates of JNK.

References

Lapadat R & Johnson GL (2002). Mitogen-activated protein kinase pathways mediated by ERK, JNK, and p38 protein kinases. Science, 298, 1911-2.

Seger R & Yoon S (2006). The extracellular signal-regulated kinase: multiple substrates regulate diverse cellular functions. Growth Factors, 24, 21-44.

Kobe B & Bogoyevitch MA (2006). Uses for JNK: the many and varied substrates of the c-Jun N-terminal kinases. Microbiol Mol Biol Rev, 70, 1061-95.

Edit history

Date	Action	Author
2009-12-16	Authored	Shamovsky V
2009-12-16	Created	Shamovsky V
2010-02-28	Edited	Shamovsky V
2010-02-28	Reviewed	Gillespie ME
2024-03-08	Modified	Wright A

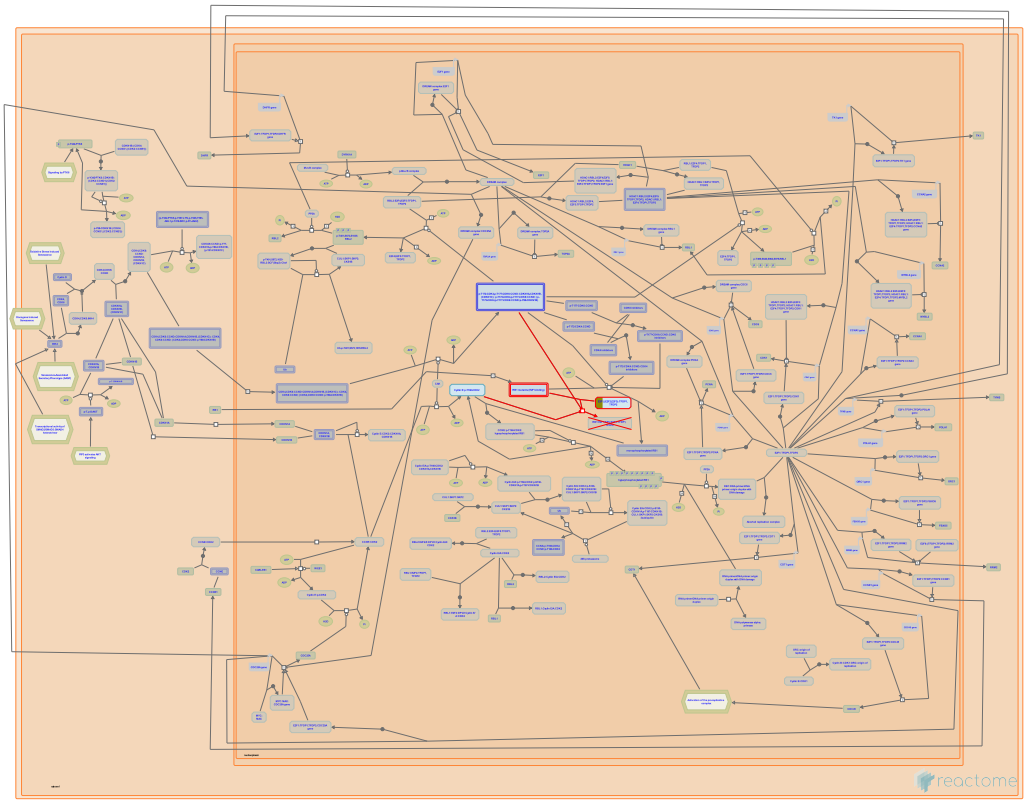
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
CREB1	P16220-1	JUN	P05412

Interactors found in this pathway (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CREB1	P16220	P05412, P18846	JUN	P05412	P05412, P18846, P15336, P01100

8. Defective binding of RB1 mutants to E2F1,(E2F2, E2F3) (R-HSA-9661069)



Cellular compartments: nucleoplasm.

Diseases: cancer.

This pathway describes impaired binding of RB1 pocket domain mutants to activating E2Fs, E2F1, E2F2 and E2F3 (Templeton et al. 1991, Helin et al. 1993, Otterson et al. 1997, Ji et al. 2004).

References

Kaye FJ, Otterson GA, Chen Wd, Coxon AB & Khleif SN (1997). Incomplete penetrance of familial retinoblastoma linked to germ-line mutations that result in partial loss of RB function. Proc. Natl. Acad. Sci. U.S.A., 94, 12036-40.

Ji P, Rekhtman K, Pagano M, Bloom J, Jiang H, Zhu L & Ichetovkin M (2004). An Rb-Skp2-p27 pathway mediates acute cell cycle inhibition by Rb and is retained in a partial-penetrance Rb mutant . Mol. Cell, 16, 47-58.

Fattaey A, Harlow E & Helin K (1993). Inhibition of E2F-1 transactivation by direct binding of the retinoblastoma protein. Mol. Cell. Biol., 13, 6501-8.

Park SH, Weinberg RA, Lanier L & Templeton DJ (1991). Nonfunctional mutants of the retinoblastoma protein are characterized by defects in phosphorylation, viral oncoprotein association, and nuclear tethering. Proc. Natl. Acad. Sci. U.S.A., 88, 3033-7.

Edit history

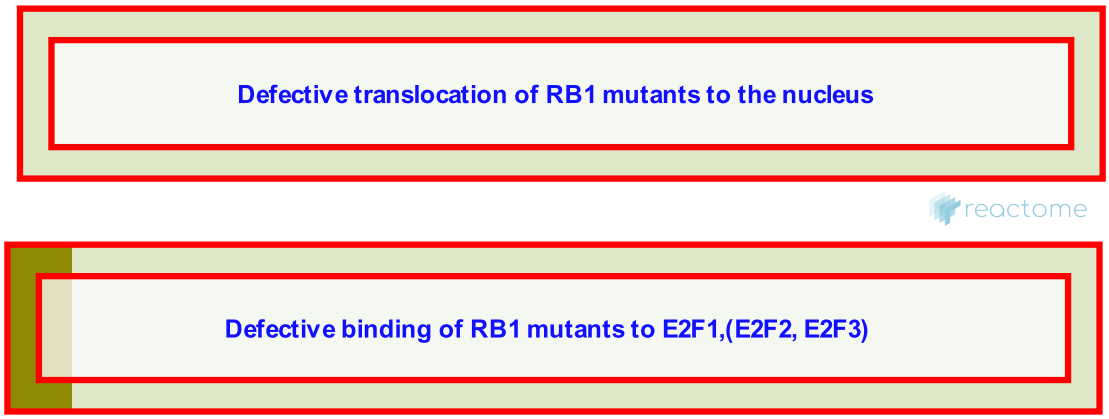
Date	Action	Author
2019-09-13	Created	Orlic-Milacic M
2020-05-07	Authored	Orlic-Milacic M

Date	Action	Author
2020-05-17	Reviewed	Dick FA
2020-05-18	Edited	Orlic-Milacic M

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

Input	UniProt Id
TFDP1	Q14186

9. Aberrant regulation of mitotic G1/S transition in cancer due to RB1 defects (R-HSA-9659787)



Diseases: cancer.

RB1 protein, also known as pRB or retinoblastoma protein, is a nuclear protein that plays a major role in the regulation of the G1/S transition during mitotic cell cycle in multicellular eukaryotes. RB1 performs this function by binding to activating E2Fs (E2F1, E2F2 and E2F3), and preventing transcriptional activation of E2F1/2/3 target genes, which include a number of genes involved in DNA synthesis. RB1 binds E2F1/2/3 through the so-called pocket region, which is formed by two parts, pocket domain A (amino acid residues 373-579) and pocket domain B (amino acid residues 640-771). Besides intact pocket domains, RB1 requires an intact nuclear localization signal (NLS) at its C-terminus (amino acid residues 860-876) to be fully functional (reviewed by Classon and Harlow 2002, Dick 2007). Functionally characterized RB1 mutations mostly affect pocket domains A and B and the NLS. RB1 mutations reported in cancer are, however, scattered over the entire RB1 coding sequence and the molecular consequences of the vast majority of these mutations have not been studied (reviewed by Dick 2007).

Many viral oncoproteins inactivate RB1 by competing with E2F1/2/3 for binding to the pocket region of RB1. RB1 protein is targeted by the large T antigen of the Simian virus 40 (SV40), the adenoviral E1A protein, and the E7 protein of oncogenic human papilloma viruses (HPVs) (reviewed by Classon and Harlow 2002).

References

Classon M & Harlow E (2002). The retinoblastoma tumour suppressor in development and cancer. Nat. Rev. Cancer, 2, 910-7.

Dick FA (2007). Structure-function analysis of the retinoblastoma tumor suppressor protein - is the whole a sum of its parts?. Cell Div, 2, 26.

Edit history

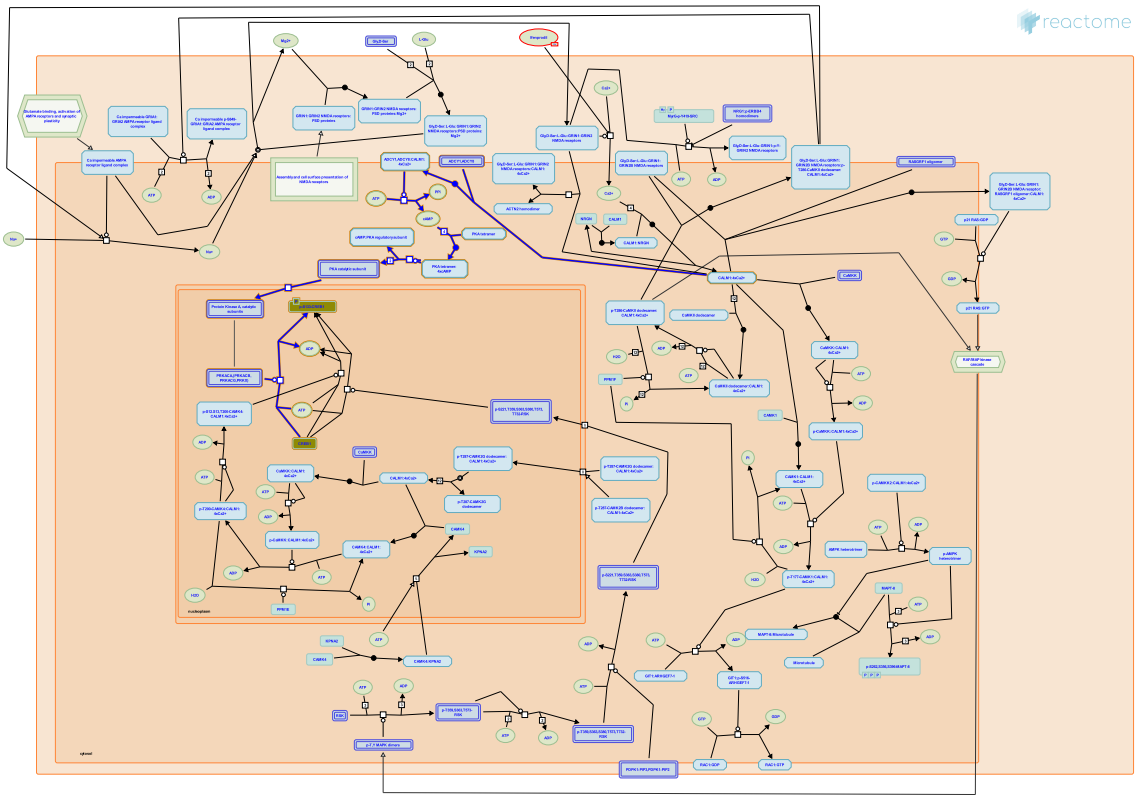
Date	Action	Author
2019-09-05	Created	Orlic-Milacic M
2020-05-07	Authored	Orlic-Milacic M
2020-05-17	Reviewed	Dick FA

Date	Action	Author
2020-05-18	Edited	Orlic-Milacic M
2023-03-08	Modified	Matthews L

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

Input	UniProt Id
TFDP1	Q14186

10. CREB1 phosphorylation through the activation of Adenylate Cyclase (R-HSA-442720)



Cellular compartments: nucleoplasm, plasma membrane, cytosol.

Ca2+ influx through activated NMDA receptors in the post synaptic neurons activates adenylate cyclase-mediated signal transduction, leading to the activation of PKA and phosphorylation and activation of CREB1 induced transcription (Masada et al. 2012, Chetkovich et al. 1991, Chetkovich and Sweatt 1993

References

Vikis HG, Lu Y, Liu Y, You M & James MA (2009). RGS17, an overexpressed gene in human lung and prostate cancer, induces tumor cell proliferation through the cyclic AMP-PKA-CREB pathway. Cancer Res, 69, 2108-16.

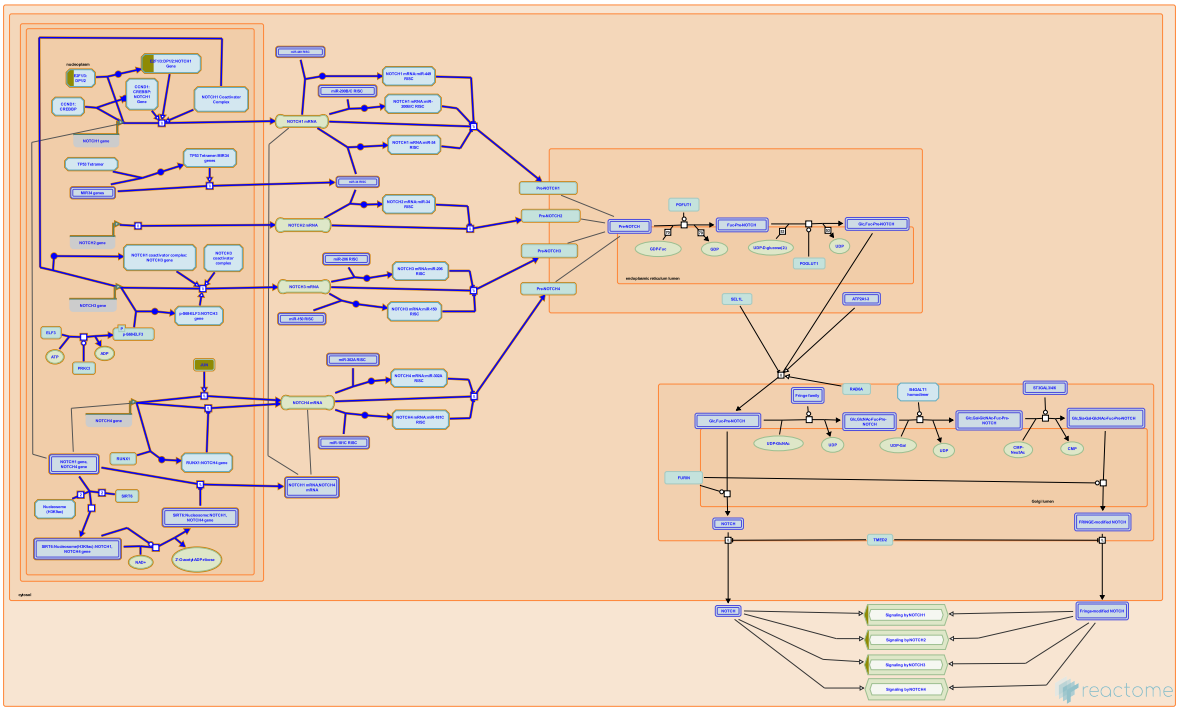
Edit history

Date	Action	Author
2009-09-29	Created	Mahajan SS
2009-10-29	Authored	Mahajan SS
2009-11-18	Reviewed	Tukey D
2009-11-19	Edited	Gillespie ME
2018-10-10	Revised	Orlic-Milacic M
2018-11-02	Reviewed	Hansen KB, Yi F
2018-11-07	Edited	Orlic-Milacic M
2024-03-08	Modified	Wright A

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

Input	UniProt Id
CREB1	P16220-1

11. Pre-NOTCH Transcription and Translation (R-HSA-1912408)



Cellular compartments: cytosol, nucleoplasm, endoplasmic reticulum membrane.

In humans, the NOTCH protein family has four members: NOTCH1, NOTCH2, NOTCH3 and NOTCH4. NOTCH1 protein was identified first, as the product of a chromosome 9 gene translocated in T-cell acute lymphoblastic leukemia that was homologous to Drosophila Notch (Ellisen et al. 1991). At the same time, rat Notch1 was cloned (Weinmaster et al. 1991), followed by cloning of mouse Notch1, named Motch (Del Amo et al. 1992). NOTCH2 protein is the product of a gene on chromosome 1 (Larsson et al. 1994). NOTCH2 expression is differentially regulated during B-cell development (Bertrand et al. 2000). NOTCH2 mutations are a rare cause of Alagille syndrome (McDaniell et al. 2006). NOTCH3 is the product of a gene on chromosome 19. NOTCH3 mutations are the underlying cause of CADASIL, cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (Joutel et al. 1996). NOTCH4, the last NOTCH protein discovered, is the product of a gene on chromosome 6 (Li et al. 1998).

MicroRNAs play an important negative role in translation and/or stability of NOTCH mRNAs. MicroRNAs miR-34 (miR-34A, miR-34B and mi-R34C), whose transcription is directly induced by the tumor suppressor protein p53 (Chang et al. 2007, Raver-Shapira et al. 2007, He et al. 2007, Corney et al. 2007) bind and negatively regulate translation of NOTCH1 mRNA (Li et al. 2009, Pang et al. 2010, Ji et al. 2009) and NOTCH2 mRNA (Li et al. 2009). NOTCH1 mRNA translation is also negatively regulated by microRNAs miR-200B and miR-200C (Kong et al. 2010), as well as miR-449A, miR-449B and miR-449C (Marcet et al. 2011). Translation of NOTCH3 mRNA is negatively regulated by microRNAs miR-150 (Ghisi et al. 2011) and miR-206 (Song et al. 2009). Translation of NOTCH4 mRNA is negatively regulated by microRNAs miR-181C (Hashimoto et al. 2010) and miR-302A (Costa et al. 2009).

Nascent NOTCH peptides are co-translationally targeted to the endoplasmic reticulum for further processing, followed by modification in the Golgi apparatus, before trafficking to the plasma membrane. Endoplasmic reticulum calcium ATPases, positively regulate NOTCH trafficking, possibly by contributing to accurate folding of NOTCH precursors (Periz et al. 1999).

References

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Edit history

Date	Action	Author
2011-09-27	Edited	Jupe S
2011-11-02	Created	Orlic-Milacic M
2011-11-14	Authored	Egan SE, Orlic-Milacic M
2012-02-06	Reviewed	Haw R
2012-02-07	Edited	D'Eustachio P
2012-02-09	Edited	May B, Gillespie ME
2012-02-11	Edited	Orlic-Milacic M
2012-05-14	Revised	Egan SE, Orlic-Milacic M
2012-05-16	Edited	D'Eustachio P
2012-05-17	Reviewed	Haw R
2017-09-20	Revised	Orlic-Milacic M
2017-10-30	Reviewed	Haw R
2017-11-02	Edited	Orlic-Milacic M
2018-04-05	Revised	Orlic-Milacic M
2018-05-01	Reviewed	Haw R
2024-03-08	Modified	Wright A

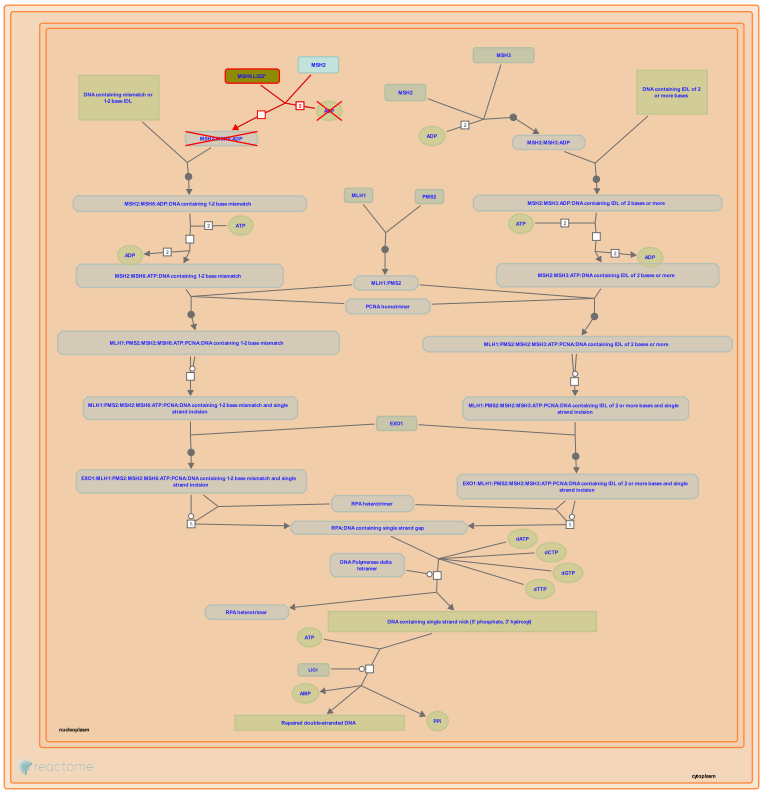
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
JUN	P05412	TFDP1	Q14186

Interactors found in this pathway (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CREB1	P16220	P05412	JUN	P05412	P05412

12. Defective Mismatch Repair Associated With MSH6 (R-HSA-5632968)



Cellular compartments: nucleoplasm.

Diseases: cancer.

MSH6 encodes a G/T mismatch-binding protein encoded by a gene localized to within 1 megabase of the related hMSH2 gene on chromosome 2. Unlike other mismatch repair genes, the MSH6 deficient cells showed alterations primarily in mononucleotide tracts, indicating the role MSH6 plays in maintaining the integrity of the human genome. Cells deficient in MSH6, accrue mutations in tracts of repeated nucleotides. MSH6 defects seem to be less common than MLH1 and MSH2 defects. They have been mostly observed in atypical HNPCC families and are characterized by a weaker family history of tumor development, higher age at disease onset, and low degrees of microsatellite instability (MSI) that predominantly involving mononucleotide runs.

References

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Edit history

Date	Action	Author
2011-11-10	Authored	Gillespie ME
2014-10-29	Created	Gillespie ME
2016-11-01	Reviewed	Arora S
2017-02-27	Edited	Gillespie ME

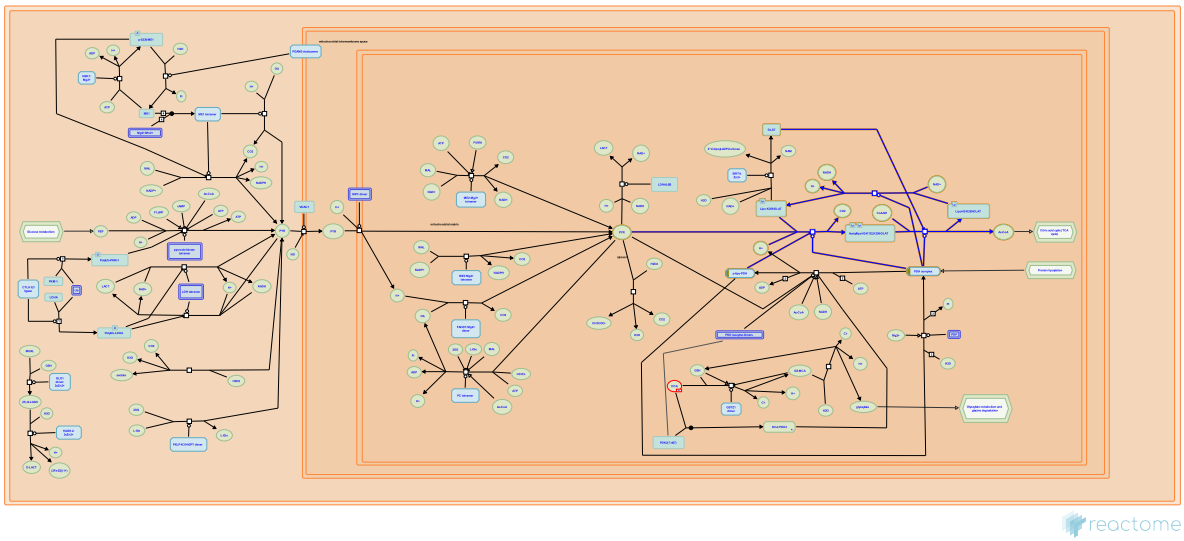
1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
MSH6	P52701

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH6	P52701	P43246			

13. PDH complex synthesizes acetyl-CoA from PYR (R-HSA-9861559)



Cellular compartments: mitochondrial inner membrane, mitochondrial matrix.

The mitochondrial pyruvate dehydrogenase complex catalyzes the reaction of pyruvate, CoASH, and NAD+ to form acetylCoA, CO2, and NADH. The enzyme complex contains multiple copies of E1 alpha, E1 beta, E2, and E3, each with distinct catalytic activities (Reed and Hackert 1990; Zhou et al 2001), and the X-component (PDHX) which is required for anchoring E3 to E2 (Hiromasa et al., 2004; Vijayakrishnan et al., 2010). The reaction starts with the oxidative decarboxylation of pyruvate catalyzed by E1 alpha and beta (pyruvate dehydrogenase). Lipoamide cofactor associated with E2 is reduced at the same time. Next, the acetyl group derived from pyruvate is transferred to coenzyme A in two steps catalyzed by E2 (DLAT, dihydrolipolyl transacetylase). Finally, the oxidized form of lipoamide is regenerated and electrons are transferred to NAD+ in two steps catalyzed by E3 (DLD, dihydrolipoyl dehydrogenase). The biochemical details of this reaction have been worked out with pyruvate dehydrogenase complex and subunits purified from bovine tissue and other non-human sources. Direct evidence for the roles of the corresponding human proteins comes from studies of patients expressing mutant forms of E1 alpha (Lissens et al. 2000), E1 beta (Brown et al. 2004), E2 (Head et al. 2005), and E3 (Brautigam et al. 2005). The most common PDH complex deficiencies are caused by defects in PDHA and PDHX but can be caused by defects in any component of the complex (e.g. Pavlu-Pereira et al., 2020; reviewed in Prasad et al., 2011).

References

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Rivera I, Ferreira AC, Tavares de Almeida I, Bandeira A, Gomes R, Sequeira S, ... Pavlu-Pereira H (2020). Pyruvate dehydrogenase complex deficiency: updating the clinical, metabolic and mutational landscapes in a cohort of Portuguese patients. Orphanet J Rare Dis, 15, 298.

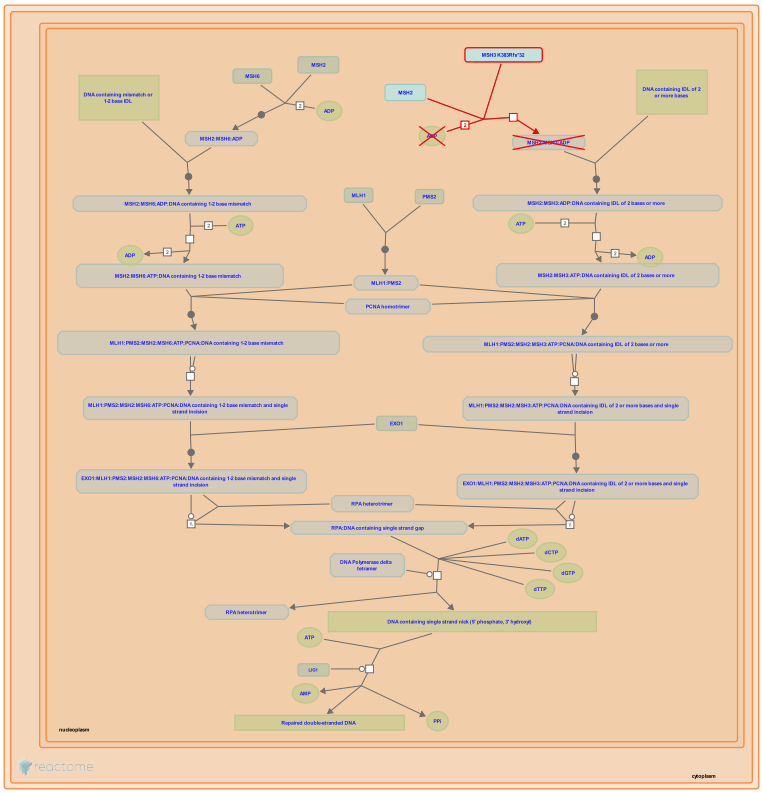
Edit history

Date	Action	Author
2024-01-25	Authored	Stephan R
2024-02-21	Created	Stephan R
2024-02-23	Edited	Stephan R
2024-02-23	Reviewed	Hill DP

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

Input	UniProt Id
PDHX	O00330

14. Defective Mismatch Repair Associated With MSH3 (R-HSA-5632927)



Cellular compartments: nucleoplasm.

Diseases: cancer.

MSH3 forms a heterodimer with MSH2 to form the MSH3:MSH2 complex, part of the post-replicative DNA mismatch repair system. This complex initiates mismatch repair by binding to a mismatch and then forming a complex with MutL alpha heterodimer. This gene contains a polymorphic 9 bp tandem repeat sequence in the first exon. Defects in this gene are a cause of susceptibility to endometrial cancer.

References

Umar A, Risinger JI, Kunkel TA, Berchuck A, Barrett JC & Boyd J (1996). Mutation of MSH3 in endometrial cancer and evidence for its functional role in heteroduplex repair. Nat. Genet., 14, 102-5.

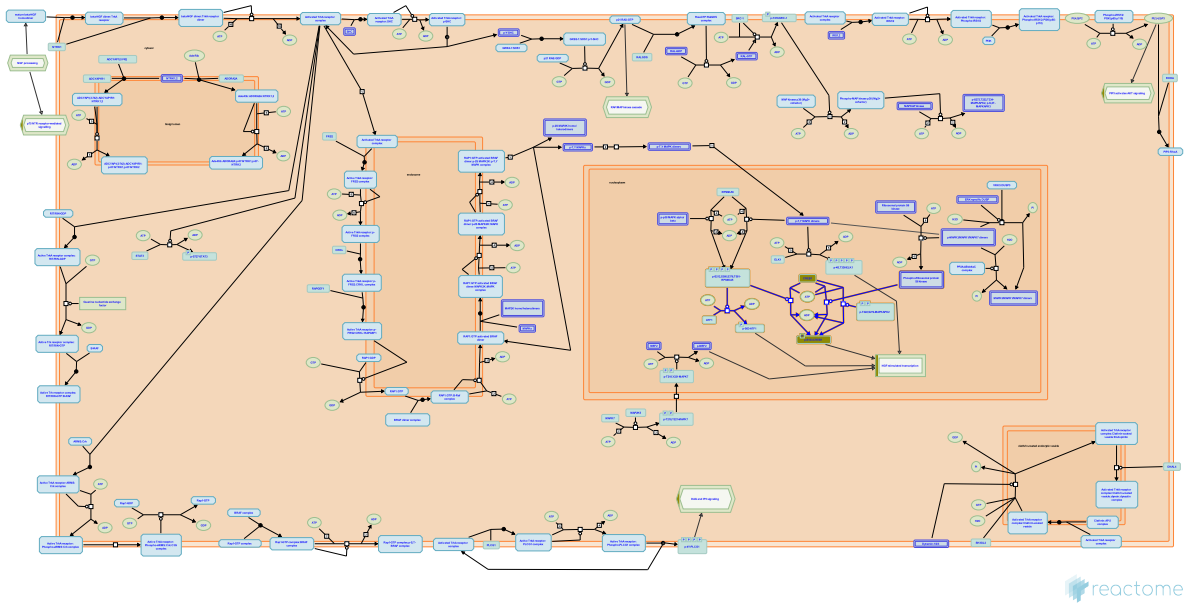
Edit history

Date	Action	Author
2011-11-10	Authored	Gillespie ME
2014-10-29	Created	Gillespie ME
2016-11-01	Reviewed	Arora S
2017-02-27	Edited	Gillespie ME
2023-03-08	Modified	Matthews L

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH6	P52701	P43246			

15. CREB phosphorylation (R-HSA-199920)



Nerve growth factor (NGF) activates multiple signalling pathways that mediate the phosphorylation of CREB at the critical regulatory site, serine 133. CREB phosphorylation at serine 133 is a crucial event in neurotrophin signalling, being mediated by ERK/RSK, ERK/MSK1 and p38/MAPKAPK2 pathways. Several kinases, such as MSK1, RSK1/2/3 (MAPKAPK1A/B/C), and MAPKAPK2, are able to directly phosphorylate CREB at S133. MSK1 is also able to activate ATF (Cyclic-AMP-dependent transcription factor). However, the NGF-induced CREB phosphorylation appears to correlate better with activation of MSK1 rather than RSK1/2/3, or MAPKAPK2. In retrograde signalling, activation of CREB occurs within 20 minutes after neurotrophin stimulation of distal axons.

References

Edit history

Date	Action	Author
2006-10-10	Authored	Annibali D, Nasi S
2007-07-13	Created	Jassal B
2007-11-08	Reviewed	Greene LA
2024-03-08	Modified	Wright A

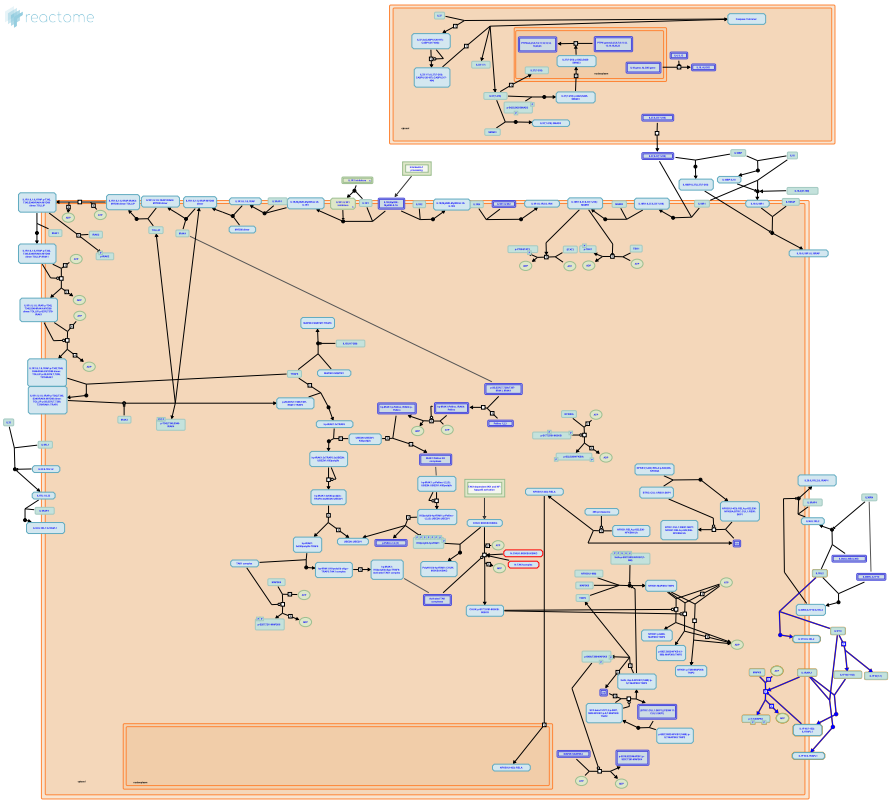
1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
CREB1	P16220-1

Interactors found in this pathway (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CREB1	P16220	P18846	JUN	P05412	P18846

16. Interleukin-38 signaling (R-HSA-9007892)



Cellular compartments: nucleoplasm, extracellular region, cytosol.

Interleukins are immunomodulatory proteins that elicit a wide array of responses in cells and tissues. Interleukin 1 family member 10 (IL1F10, IL 38) is a member of the IL1 family (Lin et al. 2001, Bensen et al. 2001). IL1F10 is selectively produced by human apoptotic cells (Mora et al. 2016) and human epidermal keratinocytes (based on mRNA studies) (Boutet M A et al. 2016). IL1F10 can bind to interleukin 1 receptor like 2 (IL1RL2) and may result in the suppression of IL 17 and IL 22 and induction of IL 6 production (van de Veerdonk et al. 2012, Mora et al. 2016). IL1F10 is synthesized as precursors that require N terminal processing to attain full receptor agonist or antagonist function (Mora et al. 2016). Both full length (1 – 152 amino acids) and N terminal truncated (20 – 152 amino acids) IL1F10 can bind Interleukin 1 receptor accessory protein like 1 (IL1RAPL1) (Mora et al. 2016). The binding affinity of truncated IL1F10 is much higher than that of the full length. However, binding of the full length or truncated forms has distinct outcomes; the former induces IL6 and the latter suppresses IL6 via JNK and AP1 signaling (Mora et al. 2016).

References

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Yuan X, Li Y, Peng X & Li M (2015). Role of IL-38 and its related cytokines in inflammation. Mediators Inflamm., 2015, 807976.

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Weigert A, Putyrski M, Frank AC, Wittig I, Brüne B, Schlemmer A, ... Mora J (2016). Interleukin-38 is released from apoptotic cells to limit inflammatory macrophage responses. J Mol Cell Biol.

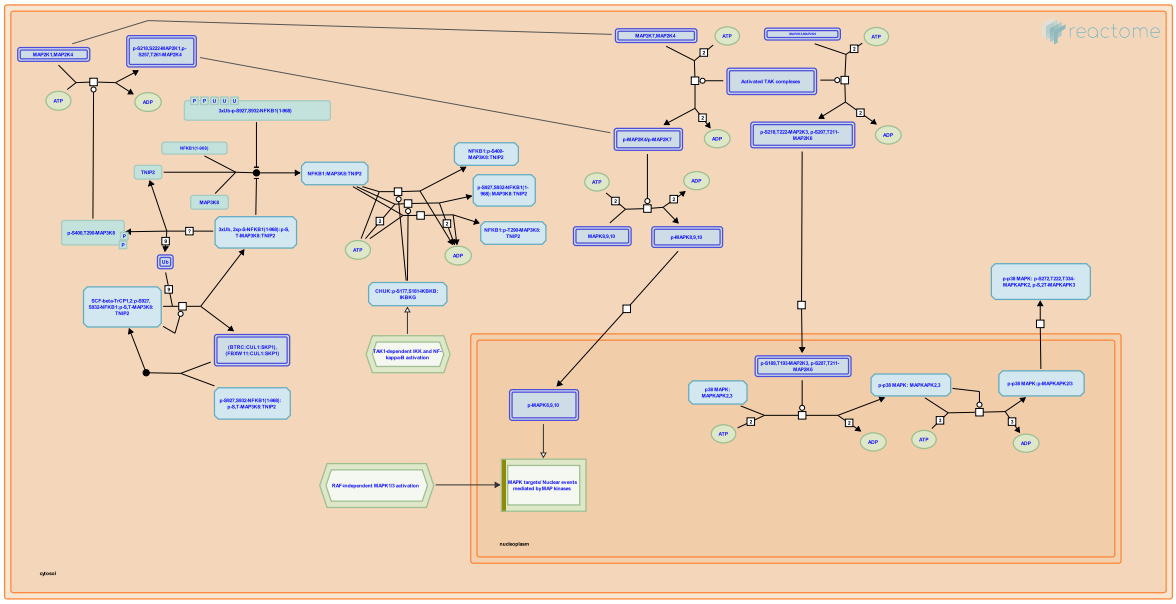
Edit history

Date	Action	Author
2017-06-06	Created	Varusai TM
2017-07-28	Reviewed	Mora J
2017-08-08	Edited	Varusai TM
2017-08-08	Authored	Varusai TM
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JUN	P05412	P45983			

17. MAP kinase activation (R-HSA-450294)



Cellular compartments: nucleoplasm, cytosol.

The mitogen activated protein kinase (MAPK) cascade, one of the most ancient and evolutionarily conserved signaling pathways, is involved in many processes of immune responses. The MAP kinases cascade transduces signals from the cell membrane to the nucleus in response to a wide range of stimuli (Chang and Karin, 2001; Johnson et al, 2002).

There are three major groups of MAP kinases
the extracellular signal-regulated protein kinases ERK1/2, the p38 MAP kinase and the c-Jun NH-terminal kinases JNK.

ERK1 and ERK2 are activated in response to growth stimuli. Both JNKs and p38-MAPK are activated in response to a variety of cellular and environmental stresses. The MAP kinases are activated by dual phosphorylation of Thr and Tyr within the tripeptide motif Thr-Xaa-Tyr. The sequence of this tripeptide motif is different in each group of MAP kinases: ERK (Thr-Glu-Tyr); p38 (Thr-Gly-Tyr); and JNK (Thr-Pro-Tyr).

MAPK activation is mediated by signal transduction in the conserved three-tiered kinase cascade: MAPKKKK (MAP4K or MKKKK or MAPKKK Kinase) activates the MAPKKK. The MAPKKKs then phosphorylates a dual-specificity protein kinase MAPKK, which in turn phosphorylates the MAPK.

The dual specificity MAP kinase kinases (MAPKK or MKK) differ for each group of MAPK. The ERK MAP kinases are activated by the MKK1 and MKK2; the p38 MAP kinases are activated by MKK3, MKK4, and MKK6; and the JNK pathway is activated by MKK4 and MKK7. The ability of MAP kinase kinases (MKKs, or MEKs) to recognize their cognate MAPKs is facilitated by a short docking motif (the D-site) in the MKK N-terminus, which binds to a complementary region on the MAPK. MAPKs then recognize many of their targets using the same strategy, because many MAPK substrates also contain D-sites.

The upstream signaling events in the TLR cascade that initiate and mediate the ERK signaling pathway remain unclear.

References

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Edit history

Date	Action	Author
2009-12-16	Authored	Shamovsky V
2009-12-16	Created	Shamovsky V
2010-02-28	Edited	Shamovsky V
2010-02-28	Reviewed	Gillespie ME
2024-03-08	Modified	Wright A

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

Input	UniProt Id	Input	UniProt Id
CREB1	P16220-1	JUN	P05412

Interactors found in this pathway (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CREB1	P16220	P05412, P18846	JUN	P05412	P05412, P18846, P15336, P01100

18. Interleukin-17 signaling (R-HSA-448424)

Interleukin-17 (IL17) is a family of cytokines (Kawaguchi et al. 2004, Gu et al. 2013). IL17A, the founding member of the family is able to induce the production of other cytokines and chemokines, such as IL6, IL8, and granulocyte colony-stimulating factor (G-CSF) in a variety of cell types, including activated T-cells. It plays a pivotal role in host defenses in response to microbial infection and is involved in the pathogenesis of autoimmune diseases and allergic syndromes. IL17 activates several downstream signaling pathways including NFkB, MAPKs and C/EBPs, inducing the expression of antibacterial peptides, proinflammatory chemokines and cytokines and matrix metalloproteases (MMPs). IL17 can stabilize the mRNA of genes induced by TNF-alpha. IL17 signal transduction is mediated by the cytosolic adaptor molecule ACT1 (also known as CIKS).

The receptor for IL17D is unknown (Gu et al. 2013).

References

Li X, Gu C & Wu L (2013). IL-17 family: cytokines, receptors and signaling. Cytokine, 64, 477-85.

Edit history

Date	Action	Author
2009-11-24	Created	Jupe S
2014-06-04	Authored	Jupe S
2016-01-28	Edited	Jupe S
2016-01-28	Reviewed	Meldal BH

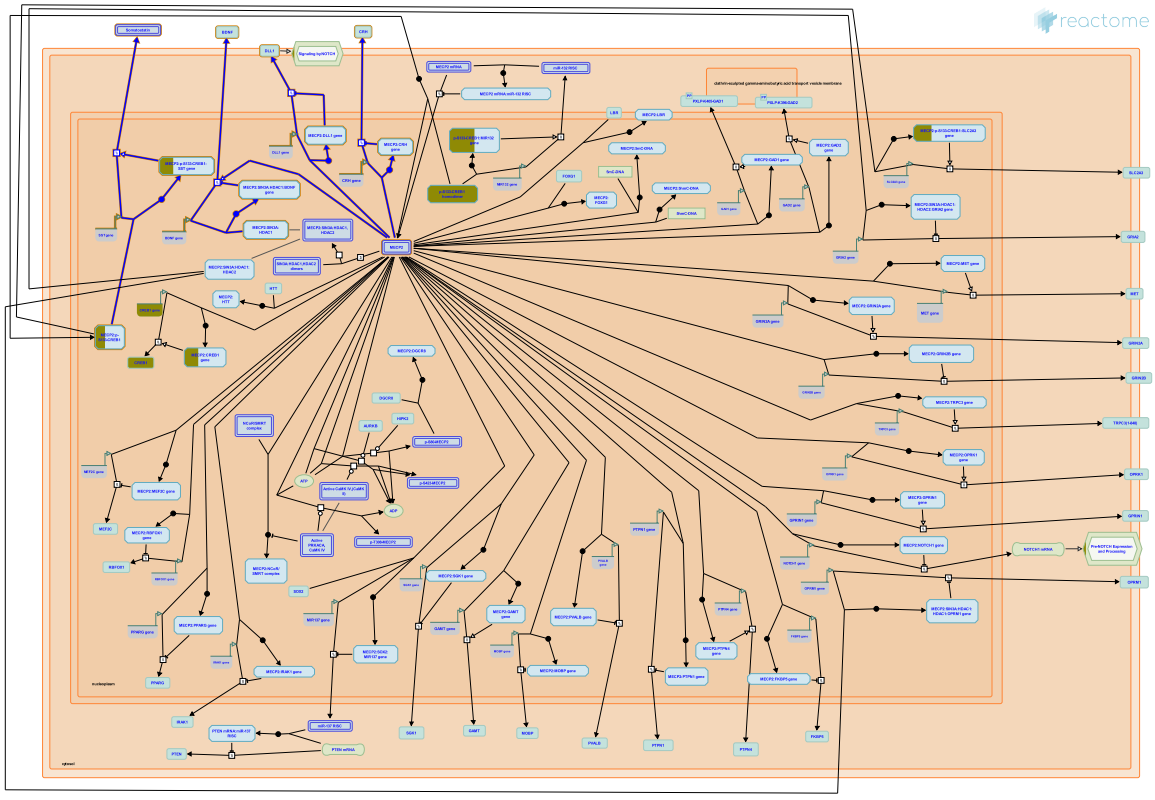
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
CREB1	P16220-1	JUN	P05412

Interactors found in this pathway (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CREB1	P16220	P05412, P18846	JUN	P05412	P05412, P18846, P15336, P01100

19. MECP2 regulates transcription of neuronal ligands (R-HSA-9022702)



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).

References

Mandel-Brehm C, Samaco RC, Zoghbi HY, McGill BE, Shaw CA & McGraw CM (2012). Crh and Oprm1 mediate anxiety-related behavior and social approach in a mouse model of MECP2 duplication syndrome. Nat. Genet., 44, 206-11.

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Zhong X, Jin P, Chau KF, Masliah J, Kong G, Chi J, ... Zhao X (2014). Cell cycle-linked MeCP2 phosphorylation modulates adult neurogenesis involving the Notch signalling pathway. Nat Commun, 5, 5601.

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Edit history

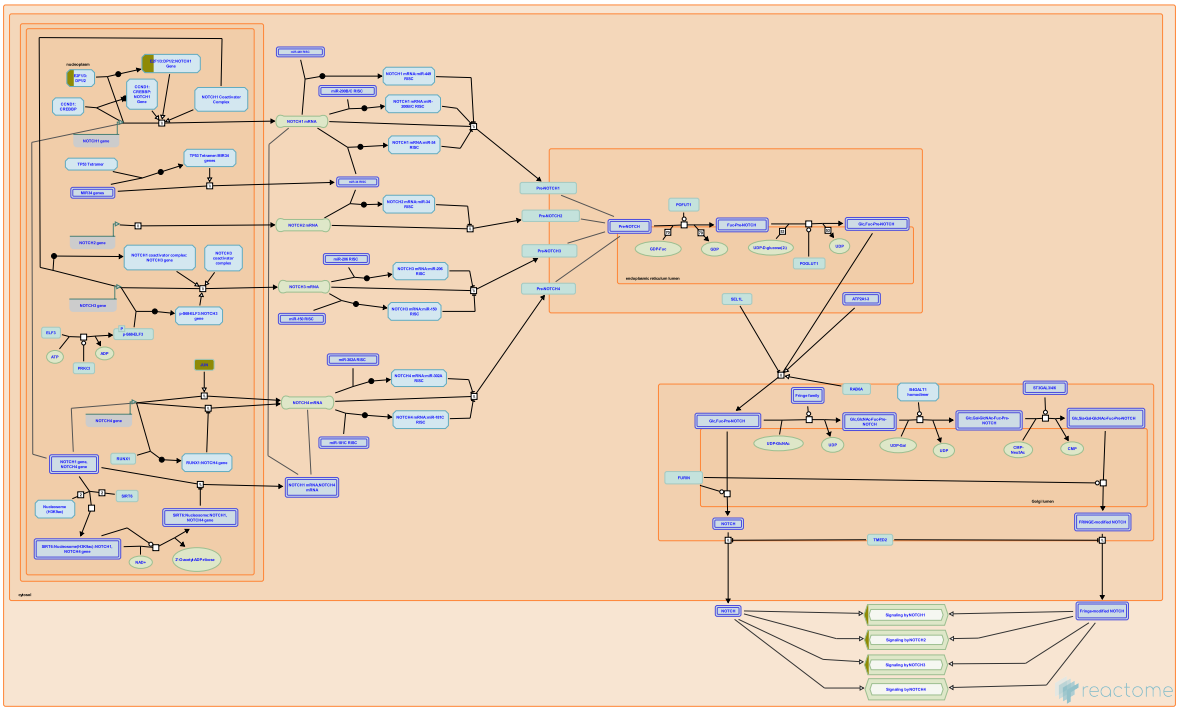
Date	Action	Author
2017-09-25	Created	Orlic-Milacic M

Date	Action	Author
2017-10-02	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2023-03-08	Modified	Matthews L

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

Input	UniProt Id
CREB1	P16220-1

20. Pre-NOTCH Expression and Processing (R-HSA-1912422)



Cellular compartments: cytosol, endoplasmic reticulum lumen, Golgi membrane, Golgi lumen, nucleoplasm, plasma membrane, endoplasmic reticulum membrane.

In humans and other mammals the NOTCH gene family has four members, NOTCH1, NOTCH2, NOTCH3 and NOTCH4, encoded on four different chromosomes. Their transcription is developmentally regulated and tissue specific, but very little information exists on molecular mechanisms of transcriptional regulation. Translation of NOTCH mRNAs is negatively regulated by a number of recently discovered microRNAs (Li et al. 2009, Pang et al.2010, Ji et al. 2009, Kong et al. 2010, Marcet et al. 2011, Ghisi et al. 2011, Song et al. 2009, Hashimoto et al. 2010, Costa et al. 2009).

The nascent forms of NOTCH precursors, Pre-NOTCH1, Pre-NOTCH2, Pre-NOTCH3 and Pre-NOTCH4, undergo extensive posttranslational modifications in the endoplasmic reticulum and Golgi apparatus to become functional. In the endoplasmic reticulum, conserved serine and threonine residues in the EGF repeats of NOTCH extracellular domain are fucosylated and glucosylated by POFUT1 and POGLUT1, respectively (Yao et al. 2011, Stahl et al. 2008, Wang et al. 2001, Shao et al. 2003, Acar et al. 2008, Fernandez Valdivia et al. 2011).

In the Golgi apparatus, fucose groups attached to NOTCH EGF repeats can be elongated by additional glycosylation steps initiated by fringe enzymes (Bruckner et al. 2000, Moloney et al. 2000, Cohen et al. 1997, Johnston et al. 1997, Chen et al. 2001). Fringe-mediated modification modulates NOTCH signaling but is not an obligatory step in Pre-NOTCH processing. Typically, processing of Pre-NOTCH in the Golgi involves cleavage by FURIN convertase (Blaumueller et al. 1997, Logeat et al. 1998, Gordon et al. 2009, Rand et al. 2000, Chan et al. 1998). The cleavage of NOTCH results in formation of mature NOTCH heterodimers that consist of NOTCH extracellular domain (NEC i.e. NECD) and NOTCH transmembrane and intracellular domain (NTM i.e. NTMICD). NOTCH heterodimers translocate to the cell surface where they function in cell to cell signaling.

References

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Edit history

Date	Action	Author
2011-11-02	Created	Orlic-Milacic M
2011-11-14	Authored	Egan SE, Orlic-Milacic M
2012-02-06	Reviewed	Haw R
2012-02-07	Edited	D'Eustachio P
2012-02-11	Edited	Orlic-Milacic M
2024-03-08	Modified	Wright A

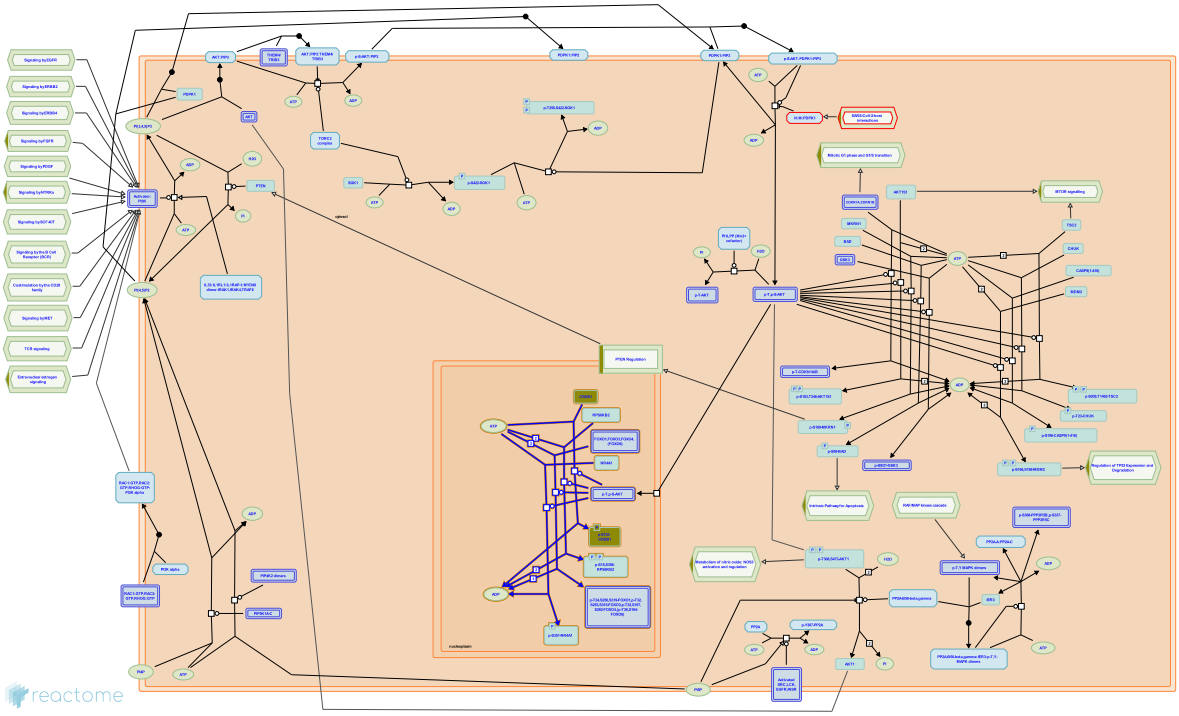
2 submitted entities found in this pathway, mapping to 2 Reactome entities

Input	UniProt Id	Input	UniProt Id
JUN	P05412	TFDP1	Q14186

Interactors found in this pathway (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CREB1	P16220	P05412	JUN	P05412	P05412

21. AKT phosphorylates targets in the nucleus (R-HSA-198693)



Cellular compartments: nucleoplasm.

After translocation into the nucleus, AKT can phosphorylate a number of targets there such as CREB, forkhead transcription factors, SRK and NUR77.

References

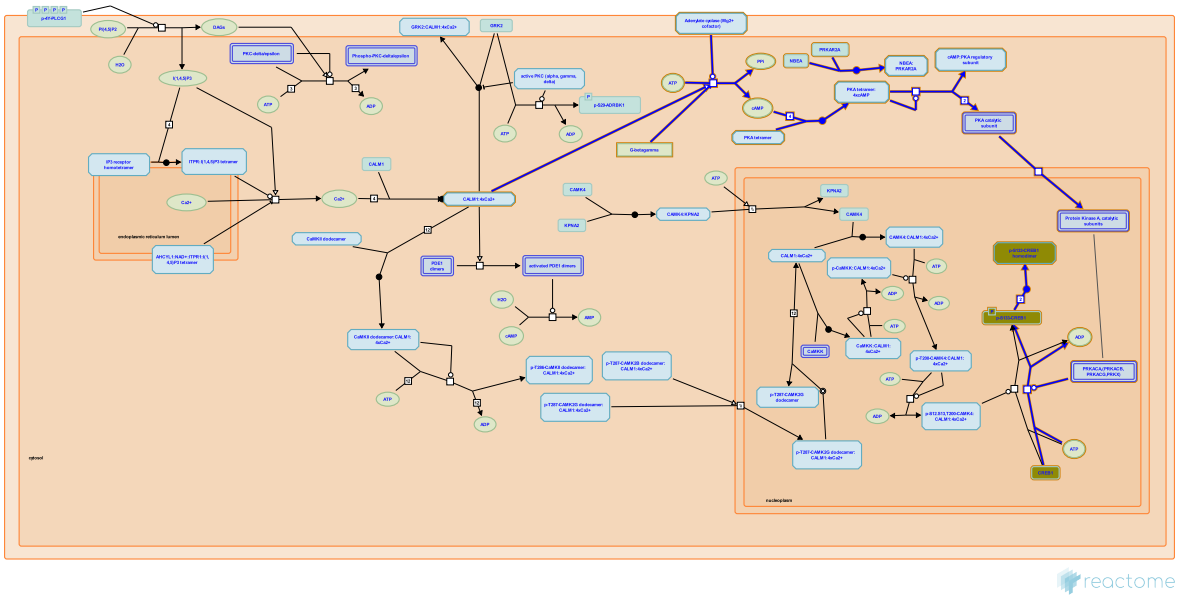
Edit history

Date	Action	Author
2006-10-10	Authored	Annibali D, Nasi S
2007-07-10	Created	
2007-11-08	Reviewed	Greene LA

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

Input	UniProt Id
CREB1	P16220-1

22. PKA-mediated phosphorylation of CREB (R-HSA-111931)



Cellular compartments: nucleoplasm, plasma membrane, cytosol.

Cyclic adenosine 3',5'-monophosphate (cAMP) induces gene transcription through activation of cAMP-dependent protein kinase (PKA), and subsequent phosphorylation of the transcription factor cAMP response element-binding protein, CREB, at serine-133.

References

Moens U, Delghandi MP & Johannessen M (2005). The cAMP signalling pathway activates CREB through PKA, p38 and MSK1 in NIH 3T3 cells. Cell Signal, 17, 1343-51.

Moens U, Delghandi MP & Johannessen M (2004). What turns CREB on?. Cell Signal, 16, 1211-27.

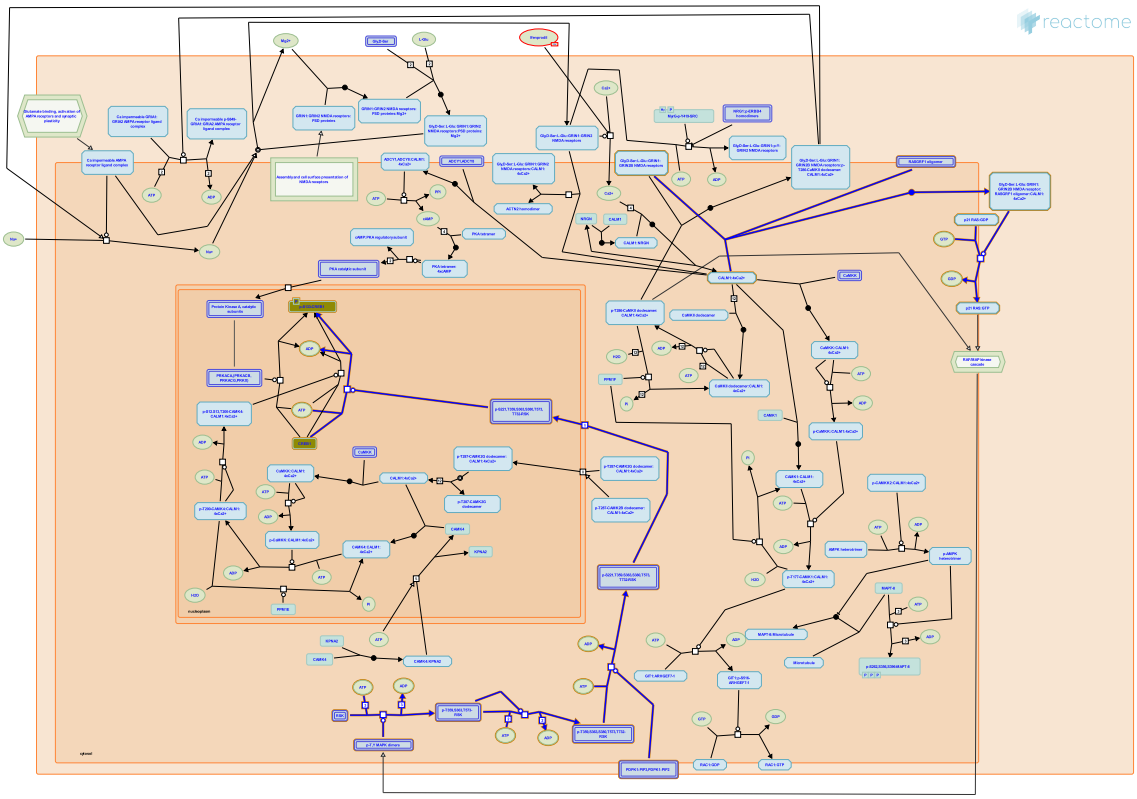
Edit history

Date	Action	Author
2004-03-25	Created	Schmidt EE
2004-03-31	Authored	Jassal B, Le Novere N
2008-11-06	Edited	Jassal B
2008-11-06	Reviewed	Castagnoli L
2024-03-08	Modified	Wright A

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

Input	UniProt Id
CREB1	P16220-1

23. CREB1 phosphorylation through NMDA receptor-mediated activation of RAS signaling (R-HSA-442742)



Cellular compartments: nucleoplasm, plasma membrane, cytosol.

Ca2+ influx through the NMDA receptor activates RAS guanyl nucleotide exchange factor RasGRF, which promotes formation of active RAS:GTP complexes (Anborgh et al. 1999, Krapivinsky et al. 2003). CaMKII, also activated by NMDA receptor-mediated Ca2+ influx, can contribute to activation of RAS/RAF/MAPK signaling by phosphorylation of RAF1 (Salzano et al. 2012). ERKs (MAPK1 and MAPK3), activated downstream of RAS signaling, phosphorylate ribosomal protein S6 kinases (RSKs), initiating activation of RSKs (reviewed by Anjum and Blenis 2012). Activated RSKs phosphorylate the transcription factor CREB1 at serine residue S133, thus stimulating CREB1-mediated transcription (De Cesare et al. 1998, Harum et al. 2001, Schinelli et al. 2001, Song et al. 2003).

References

Weeber EJ & Sweatt JD (2003). Genetics of childhood disorders: LII. Learning and memory, part 5: human cognitive disorders and the ras/ERK/CREB pathway. J Am Acad Child Adolesc Psychiatry , 42, 873-6.

Edit history

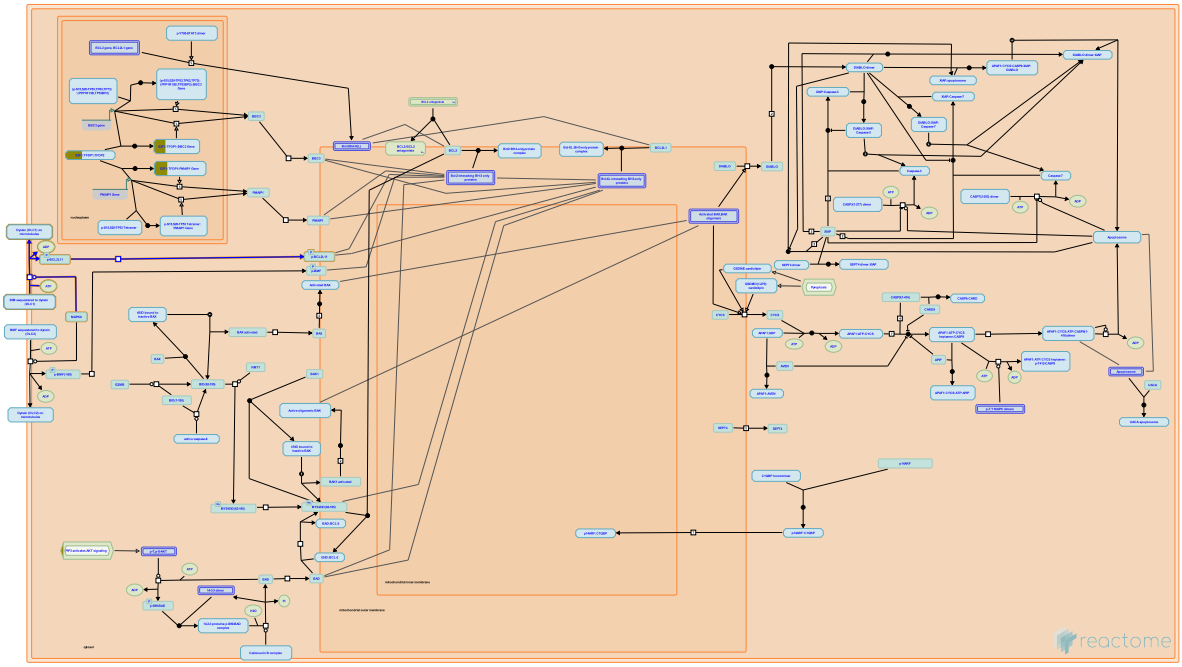
Date	Action	Author
2009-09-29	Created	Mahajan SS
2009-10-29	Authored	Mahajan SS
2009-11-18	Reviewed	Tukey D
2009-11-19	Edited	Gillespie ME
2018-11-02	Reviewed	Hansen KB, Yi F

Date	Action	Author
2018-11-07	Edited	Orlic-Milacic M

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

Input	UniProt Id
CREB1	P16220-1

24. Activation of BIM and translocation to mitochondria (R-HSA-111446)



Cellular compartments: cytosol.

BIM acts as a sentinel to check the integrity of the cytoskeleton. It exists as two variant proteins: BIM-EL and BIM-L. In healthy cells, these two isoforms are sequestered to the dynein motor complex on microtubules via the dynein light chain DLC1. JNK or MAPK8 releases BIM in response to UV irradiation by phosphorylation.

References

Vazquez A, Leprince C, Auffredou MT, Leca G, Bourgeade MF, Besnault L & Mouhamad S (2004). B cell receptor-mediated apoptosis of human lymphocytes is associated with a new regulatory pathway of Bim isoform expression. J Immunol, 172, 2084-91.

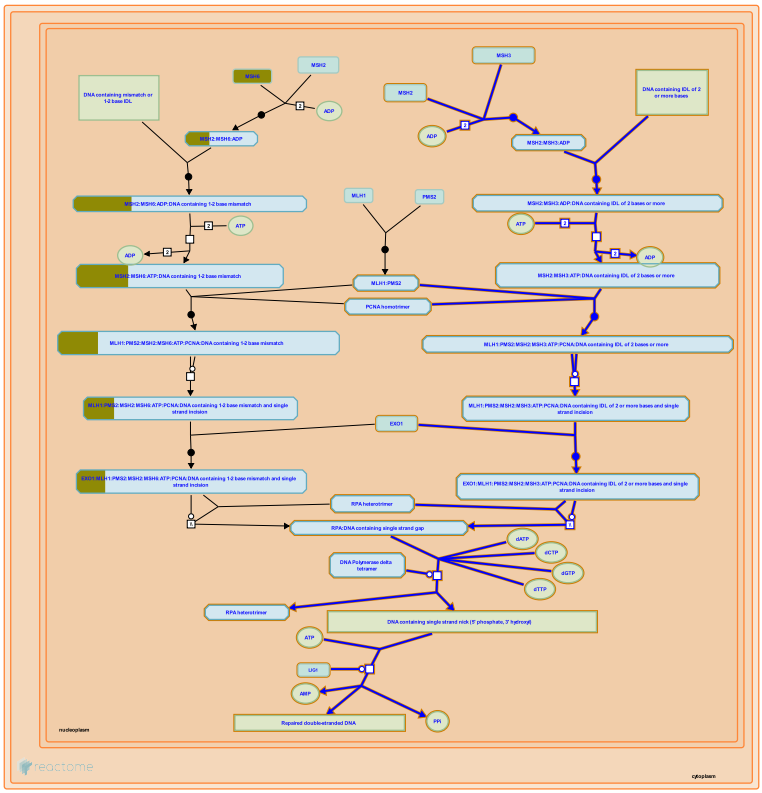
Edit history

Date	Action	Author
2004-08-09	Created	Tsujimoto Y, Hardwick JM
2004-08-20	Authored	Gopinathrao G
2024-03-06	Reviewed	Vaux DL
2024-03-07	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JUN	P05412	P45983			

25. Mismatch repair (MMR) directed by MSH2:MSH3 (MutSbeta) (R-HSA-5358606)



MSH2:MSH3 (MutSbeta) binds unpaired loops of 2 or more nucleotides (Palombo et al. 1996, Genschel et al. 1998). Human cells contain about 6-fold more MSH2:MSH6 than MSH2:MSH3 (MutSbeta) and an imbalance in the ratio can cause a mutator phenotype (Drummond et al. 1997, Marra et al. 1998). Binding of the mismatch activates MSH2:MSH3 to exchange ADP for ATP, adopt the conformation to allow movement along the DNA, and interact with downstream effectors PCNA, MLH1:PMS2 and EXO1. The interaction with PCNA initiates excision of the recently replicated strand. MLH1:PMS2 makes a nick that is enlarged to a gap of hundreds of nucleotides by EXO1. DNA is polymerized across the gap by DNA polymerase delta and the remaining nick is sealed by DNA ligase I.

References

Marti TM, Fleck O & Kunz C (2002). DNA mismatch repair and mutation avoidance pathways. J. Cell. Physiol., 191, 28-41.

Jiricny J, Iaccarino I, Palombo F, Shimada T, Nakajima E & Ikejima M (1996). hMutSbeta, a heterodimer of hMSH2 and hMSH3, binds to insertion/deletion loops in DNA. Curr. Biol., 6, 1181-4.

Drummond JT, Littman SJ, Genschel J & Modrich P (1998). Isolation of MutSbeta from human cells and comparison of the mismatch repair specificities of MutSbeta and MutSalpha. J. Biol. Chem., 273, 19895-901.

Jiricny J, Roscilli G, Iaccarino I, Marra G, Lettieri T & Delmastro P (1998). Mismatch repair deficiency associated with overexpression of the MSH3 gene. Proc. Natl. Acad. Sci. U.S.A., 95, 8568-73.

Drummond JT, Genschel J, Wolf E & Modrich P (1997). DHFR/MSH3 amplification in methotrexate-resistant cells alters the hMutSalpha/hMutSbeta ratio and reduces the efficiency of base-base mismatch repair. Proc. Natl. Acad. Sci. U.S.A., 94, 10144-9.

Edit history

Date	Action	Author
2014-03-28	Edited	May B
2014-03-28	Authored	May B
2014-03-30	Created	May B
2014-05-23	Reviewed	Edelbrock MA
2024-03-08	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
MSH6	P52701	P43246			

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.

7 of the submitted entities were found, mapping to 8 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CREB1	P16220-1	DDX3X	O00571	JUN	P05412
MSH6	P52701	PDHX	O00330	TFDP1	Q14186
TIAL1	Q01085				

Input	Ensembl Id
CREB1	ENSG00000118260

Interactors (8)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
CREB1	P16220	P05412, P18846	DDX3X	O00571	P67809
FAM154B	Q658L1	Q14192	JUN	P05412	P78563
MSH6	P52701	P43246	PDHX	O00330	Q8IWL3
TFDP1	Q14186	P06400	TIAL1	Q01085-2	Q9Y5V3

7. Identifiers not found

These 1 identifiers were not found neither mapped to any entity in Reactome.

SECISBP2L