



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 79 on 26/02/2022. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMjAyMjYxODM5NDrfMTc0Mjk%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:

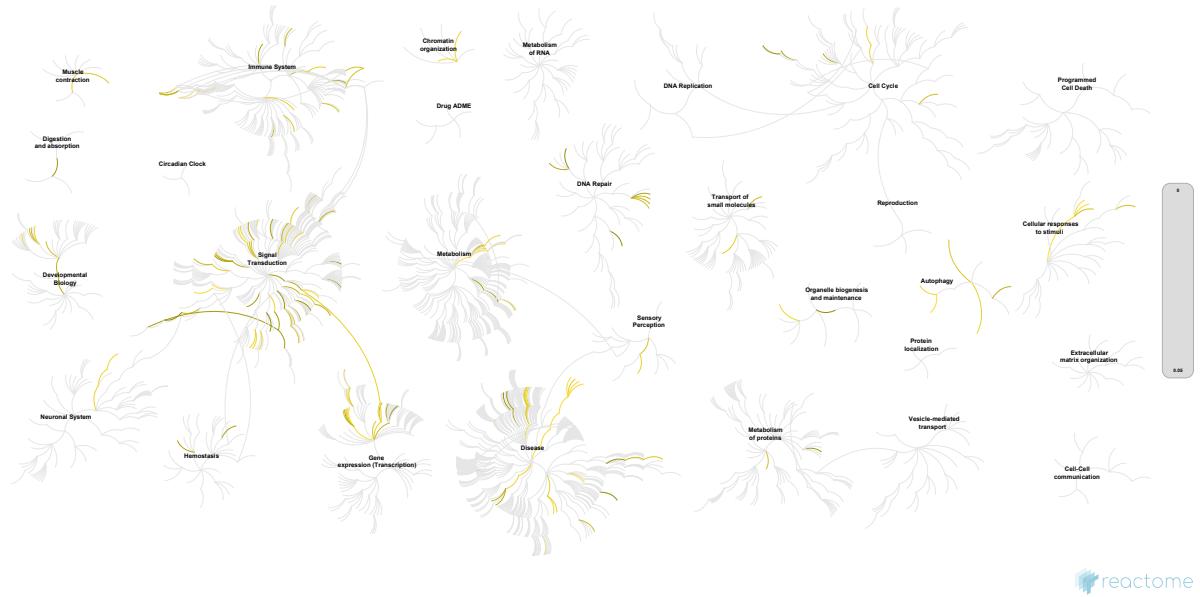
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 223 out of 382 identifiers in the sample were found in Reactome, where 1102 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 MjAyMjAyMjYxODM5NDRfMTc0Mjk%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
Oncogene Induced Senescence	9 / 42	0.003	5.52e-06	0.006	13 / 19	0.001
Oxidative Stress Induced Senescence	14 / 114	0.008	9.77e-06	0.006	16 / 40	0.003
Transcriptional Regulation by MECP2	12 / 100	0.007	5.19e-05	0.021	73 / 77	0.006
Chaperone Mediated Autophagy	6 / 23	0.002	7.08e-05	0.021	15 / 19	0.001
Regulation of MECP2 expression and activity	7 / 39	0.003	1.80e-04	0.043	12 / 14	0.001
Modulation by Mtb of host immune system	4 / 11	7.30e-04	3.42e-04	0.054	2 / 6	4.40e-04
Cellular Senescence	16 / 200	0.013	3.50e-04	0.054	32 / 90	0.007
Regulation of insulin secretion	11 / 106	0.007	3.61e-04	0.054	20 / 34	0.002
Integration of energy metabolism	13 / 145	0.01	4.36e-04	0.058	40 / 62	0.005
G alpha (z) signalling events	8 / 63	0.004	6.30e-04	0.064	13 / 13	9.53e-04
MECP2 regulates transcription of neuronal ligands	4 / 13	8.63e-04	6.38e-04	0.064	8 / 8	5.86e-04
Regulation of TP53 Activity through Methylation	5 / 23	0.002	6.49e-04	0.064	3 / 12	8.79e-04
Glucagon-like Peptide-1 (GLP1) regulates insulin secretion	7 / 50	0.003	7.79e-04	0.071	8 / 11	8.06e-04
PKA-mediated phosphorylation of key metabolic factors	3 / 7	4.64e-04	0.001	0.077	5 / 5	3.66e-04
FLT3 signaling by CBL mutants	3 / 7	4.64e-04	0.001	0.077	1 / 1	7.33e-05
Loss of phosphorylation of MECP2 at T308	3 / 7	4.64e-04	0.001	0.077	1 / 1	7.33e-05
Glucagon signaling in metabolic regulation	6 / 40	0.003	0.001	0.077	6 / 6	4.40e-04
Loss of function of MECP2 in Rett syndrome	4 / 16	0.001	0.001	0.077	5 / 5	3.66e-04
Disorders of Developmental Biology	4 / 16	0.001	0.001	0.077	5 / 5	3.66e-04
Pervasive developmental disorders	4 / 16	0.001	0.001	0.077	5 / 5	3.66e-04
Disorders of Nervous System Development	4 / 16	0.001	0.001	0.077	5 / 5	3.66e-04
GPER1 signaling	7 / 56	0.004	0.001	0.078	9 / 10	7.33e-04
NOTCH1 Intracellular Domain Regulates Transcription	7 / 57	0.004	0.002	0.078	14 / 18	0.001
Loss of MECP2 binding ability to 5hmC-DNA	2 / 2	1.33e-04	0.002	0.078	1 / 1	7.33e-05

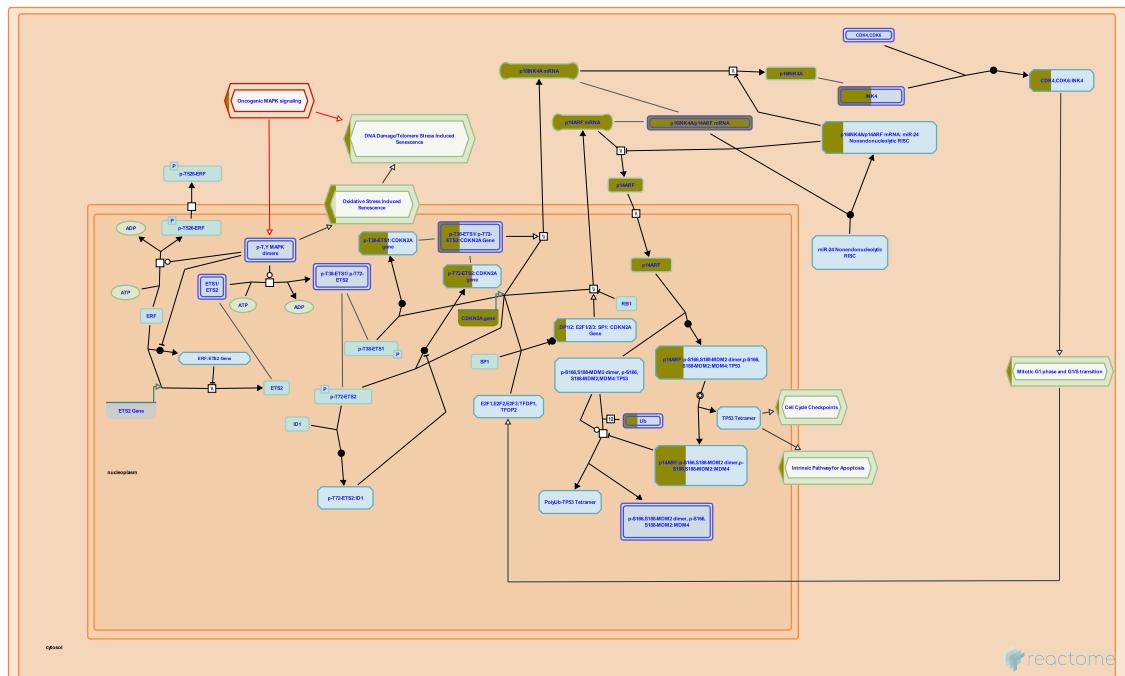
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Loss of MECP2 binding ability to the NCoR/SMRT complex	3 / 8	5.31e-04	0.002	0.078	1 / 1	7.33e-05

* 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. Oncogene Induced Senescence (R-HSA-2559585)



Oncogene-induced senescence (OIS) is triggered by high level of RAS/RAF/MAPK signaling that can be caused, for example, by oncogenic mutations in RAS or RAF proteins, or by oncogenic mutations in growth factor receptors, such as EGFR, that act upstream of RAS/RAF/MAPK cascade. Oncogene-induced senescence can also be triggered by high transcriptional activity of E2F1, E2F2 or E2F3 which can be caused, for example, by the loss-of-function of RB1 tumor suppressor.

Oncogenic signals trigger transcription of CDKN2A locus tumor suppressor genes: p16INK4A and p14ARF. p16INK4A and p14ARF share exons 2 and 3, but are expressed from different promoters and use different reading frames (Quelle et al. 1995). Therefore, while their mRNAs are homologous and are both translationally inhibited by miR-24 microRNA (Lal et al. 2008, To et al. 2012), they share no similarity at the amino acid sequence level and perform distinct functions in the cell. p16INK4A acts as the inhibitor of cyclin-dependent kinases CDK4 and CDK6 which phosphorylate and inhibit RB1 protein thereby promoting G1 to S transition and cell cycle progression (Serrano et al. 1993). Increased p16INK4A level leads to hypophosphorylation of RB1, allowing RB1 to inhibit transcription of E2F1, E2F2 and E2F3-target genes that are needed for cell cycle progression, which results in cell cycle arrest in G1 phase. p14-ARF binds and destabilizes MDM2 ubiquitin ligase (Zhang et al. 1998), responsible for ubiquitination and degradation of TP53 (p53) tumor suppressor protein (Wu et al. 1993, Fuchs et al. 1998, Fang et al. 2000). Therefore, increased p14-ARF level leads to increased level of TP53 and increased expression of TP53 target genes, such as p21, which triggers p53-mediated cell cycle arrest and, depending on other factors, may also lead to p53-mediated apoptosis. CDKN2B locus, which encodes an inhibitor of CDK4 and CDK6, p15INK4B, is located in the vicinity of CDKN2A locus, at the chromosome band 9p21. p15INK4B, together with p16INK4A, contributes to senescence of human T-lymphocytes (Erickson et al. 1998) and mouse fibroblasts (Malumbres et al. 2000). SMAD3, activated by TGF-beta-1 signaling, controls senescence in the mouse multistage carcinogenesis model through regulation of MYC and p15INK4B gene expression (Vijayachandra et al. 2003). TGF-beta-induced p15INK4B expression is also important for the senescence of hepatocellular carcinoma cell lines (Senturk et al. 2010).

MAP kinases MAPK1 (ERK2) and MAPK3 (ERK1), which are activated by RAS signaling, phosphorylate ETS1 and ETS2 transcription factors in the nucleus (Yang et al. 1996, Seidel et al. 2002, Foulds et al. 2004, Nelson et al. 2010). Phosphorylated ETS1 and ETS2 are able to bind RAS response elements (RREs) in the CDKN2A locus and stimulate p16INK4A transcription (Ohtani et al. 2004). At the same time, activated ERKs (MAPK1 i.e. ERK2 and MAPK3 i.e. ERK1) phosphorylate ERF, the repressor of ETS2 transcription, which leads to translocation of ERF to the cytosol and increased transcription of ETS2 (Sgouras et al. 1995, Le Gallic et al. 2004). ETS2 can be sequestered and inhibited by binding to ID1, resulting in inhibition of p16INK4A transcription (Ohtani et al. 2004).

Transcription of p14ARF is stimulated by binding of E2F transcription factors (E2F1, E2F2 or E2F3) in complex with SP1 to p14ARF promoter (Parisi et al. 2002).

Oncogenic RAS signaling affects mitochondrial metabolism through an unknown mechanism, leading to increased generation of reactive oxygen species (ROS), which triggers oxidative stress induced senescence pathway. In addition, increased rate of cell division that is one of the consequences of oncogenic signaling, leads to telomere shortening which acts as another senescence trigger.

While OIS has been studied to considerable detail in cultured cells, establishment of in vivo role of OIS has been difficult due to lack of specific biomarkers and its interconnectedness with other senescence pathways (Baek and Ryeom 2017, reviewed in Sharpless and Sherr 2015).

References

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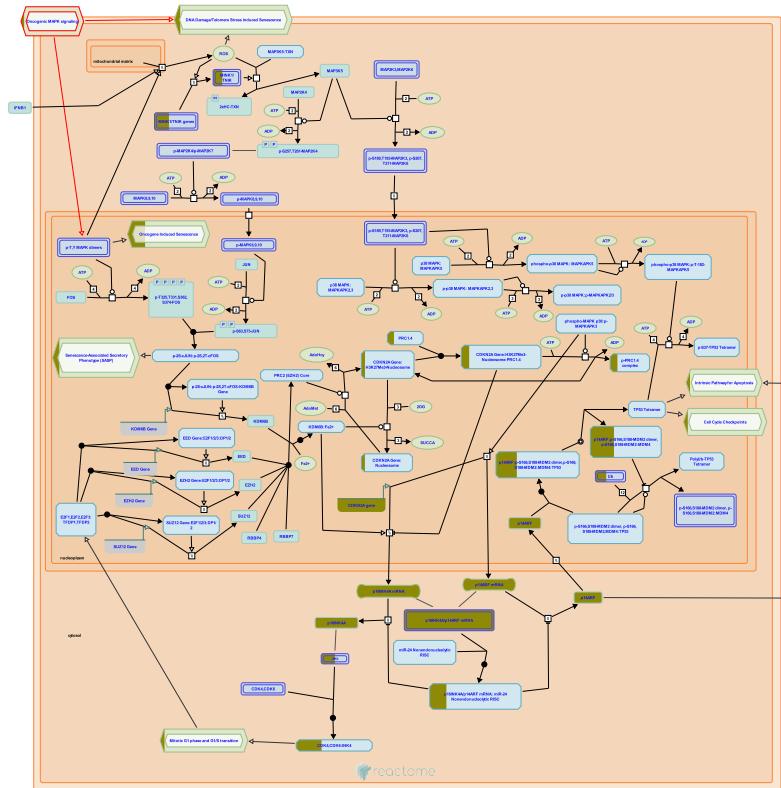
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Date	Action	Author
2012-11-02	Created	Orlic-Milacic M
2013-07-15	Edited	Matthews L, D'Eustachio P
2013-07-15	Authored	Orlic-Milacic M
2013-09-03	Reviewed	Samarajiwa S
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
CDKN2A	P42771, P42772, Q8N726	UBB	P0CG47, P62979, P62987
Input	Ensembl Id		
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755		

2. Oxidative Stress Induced Senescence (R-HSA-2559580)



Oxidative stress, caused by increased concentration of reactive oxygen species (ROS) in the cell, can happen as a consequence of mitochondrial dysfunction induced by the oncogenic RAS (Moiseeva et al. 2009) or independent of oncogenic signaling. Prolonged exposure to interferon-beta (IFNB, IFN-beta) also results in ROS increase (Moiseeva et al. 2006). ROS oxidize thioredoxin (TXN), which causes TXN to dissociate from the N-terminus of MAP3K5 (ASK1), enabling MAP3K5 to become catalytically active (Saitoh et al. 1998). ROS also stimulate expression of Ste20 family kinases MINK1 (MINK) and TNIK through an unknown mechanism, and MINK1 and TNIK positively regulate MAP3K5 activation (Nicke et al. 2005).

MAP3K5 phosphorylates and activates MAP2K3 (MKK3) and MAP2K6 (MKK6) (Ichijo et al. 1997, Takekawa et al. 2005), which act as p38 MAPK kinases, as well as MAP2K4 (SEK1) (Ichijo et al. 1997, Matsuura et al. 2002), which, together with MAP2K7 (MKK7), acts as a JNK kinase.

MKK3 and MKK6 phosphorylate and activate p38 MAPK alpha (MAPK14) and beta (MAPK11) (Raingeaud et al. 1996), enabling p38 MAPKs to phosphorylate and activate MAPKAPK2 (MK2) and MAPKAPK3 (MK3) (Ben-Levy et al. 1995, Clifton et al. 1996, McLaughlin et al. 1996, Sithanandam et al. 1996, Meng et al. 2002, Lukas et al. 2004, White et al. 2007), as well as MAPKAPK5 (PRAK) (New et al. 1998 and 2003, Sun et al. 2007).

Phosphorylation of JNKs (MAPK8, MAPK9 and MAPK10) by MAP3K5-activated MAP2K4 (Deacon and Blank 1997, Fleming et al. 2000) allows JNKs to migrate to the nucleus (Mizukami et al. 1997) where they phosphorylate JUN. Phosphorylated JUN binds FOS phosphorylated by ERK1 or ERK2, downstream of activated RAS (Okazaki and Sagata 1995, Murphy et al. 2002), forming the activated protein 1 (AP-1) complex (FOS:JUN heterodimer) (Glover and Harrison 1995, Ainbinder et al. 1997).

Activation of p38 MAPKs and JNKs downstream of MAP3K5 (ASK1) ultimately converges on transcriptional regulation of CDKN2A locus. In dividing cells, nucleosomes bound to the CDKN2A locus are trimethylated on lysine residue 28 of histone H3 (HIST1H3A) by the Polycomb repressor complex 2 (PRC2), creating the H3K27Me3 (Me3K-28-HIST1H3A) mark (Bracken et al. 2007, Kotake et al. 2007). The expression of Polycomb constituents of PRC2 (Kuzmichev et al. 2002) - EZH2, EED and SUZ12 - and thereby formation of the PRC2, is positively regulated in growing cells by E2F1, E2F2 and E2F3 (Weinmann et al. 2001, Bracken et al. 2003). H3K27Me3 mark serves as a docking site for the Polycomb repressor complex 1 (PRC1) that contains BMI1 (PCGF4) and is therefore named PRC1.4, leading to the repression of transcription of p16INK4A and p14ARF from the CDKN2A locus, where PRC1.4 mediated repression of p14ARF transcription in humans may be context dependent (Voncken et al. 2005, Dietrich et al. 2007, Agherbi et al. 2009, Gao et al. 2012). MAPKAPK2 and MAPKAPK3, activated downstream of the MAP3K5-p38 MAPK cascade, phosphorylate BMI1 of the PRC1.4 complex, leading to dissociation of PRC1.4 complex from the CDKN2A locus and upregulation of p14ARF transcription (Voncken et al. 2005). AP-1 transcription factor, formed as a result of MAP3K5-JNK signaling, as well as RAS signaling, binds the promoter of KDM6B (JMJD3) gene and stimulates KDM6B expression. KDM6B is a histone demethylase that removes H3K27Me3 mark i.e. demethylates lysine K28 of HIST1H3A, thereby preventing PRC1.4 binding to the CDKN2A locus and allowing transcription of p16INK4A (Agger et al. 2009, Barradas et al. 2009, Lin et al. 2012).

p16INK4A inhibits phosphorylation-mediated inactivation of RB family members by CDK4 and CDK6, leading to cell cycle arrest (Serrano et al. 1993). p14ARF inhibits MDM2-mediated degradation of TP53 (p53) (Zhang et al. 1998), which also contributes to cell cycle arrest in cells undergoing oxidative stress. In addition, phosphorylation of TP53 by MAPKAPK5 (PRAK) activated downstream of MAP3K5-p38 MAPK signaling, activates TP53 and contributes to cellular senescence (Sun et al. 2007).

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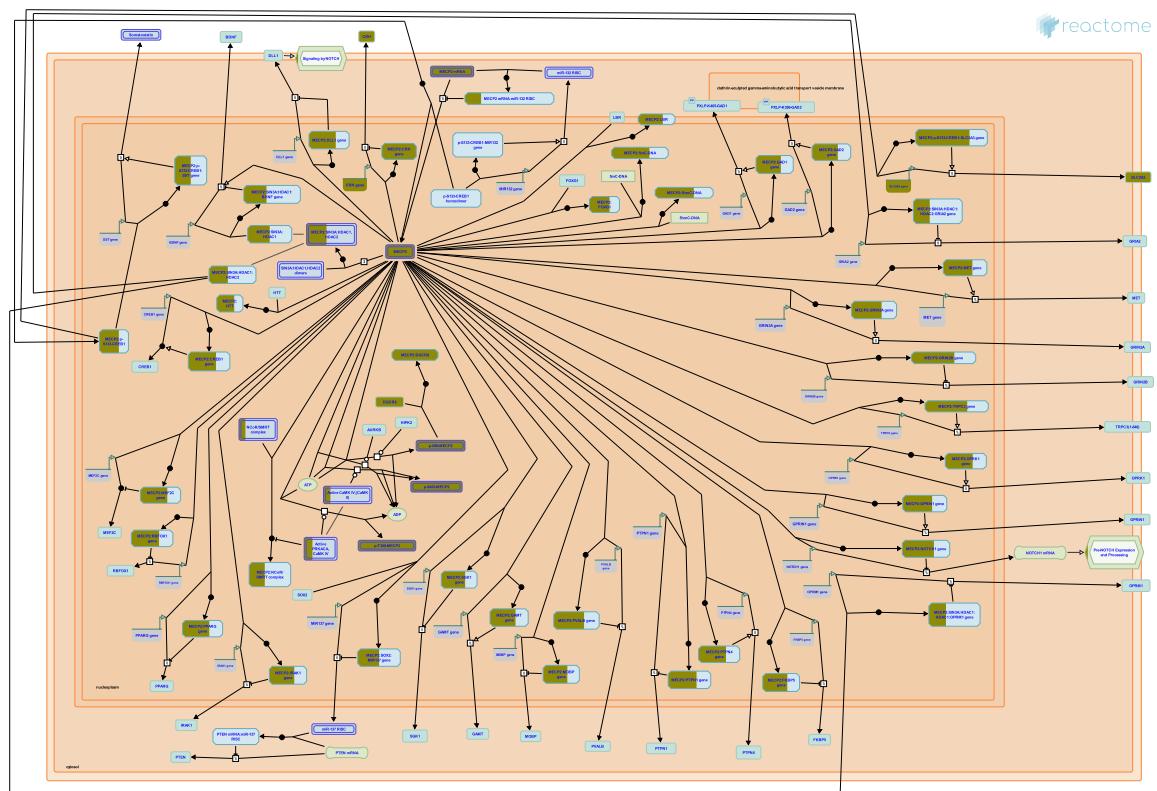
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2013-07-15	Authored	Orlic-Milacic M

Date	Action	Author
2013-09-03	Reviewed	Samarajiwa S
2021-11-28	Modified	Weiser JD

6 submitted entities found in this pathway, mapping to 14 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CBX6	O95503	CDKN2A	P42771, P42772, Q8N726	HIST1H4E	P62805
MINK1	Q8N4C8	SCMH1	Q96GD3-2	UBB	P0CG47, P62979, P62987
Input	Ensembl Id			Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755			MINK1	ENSG00000141503

3. Transcriptional Regulation by MECP2 ([R-HSA-8986944](#))



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

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

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

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

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

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

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

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

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

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

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

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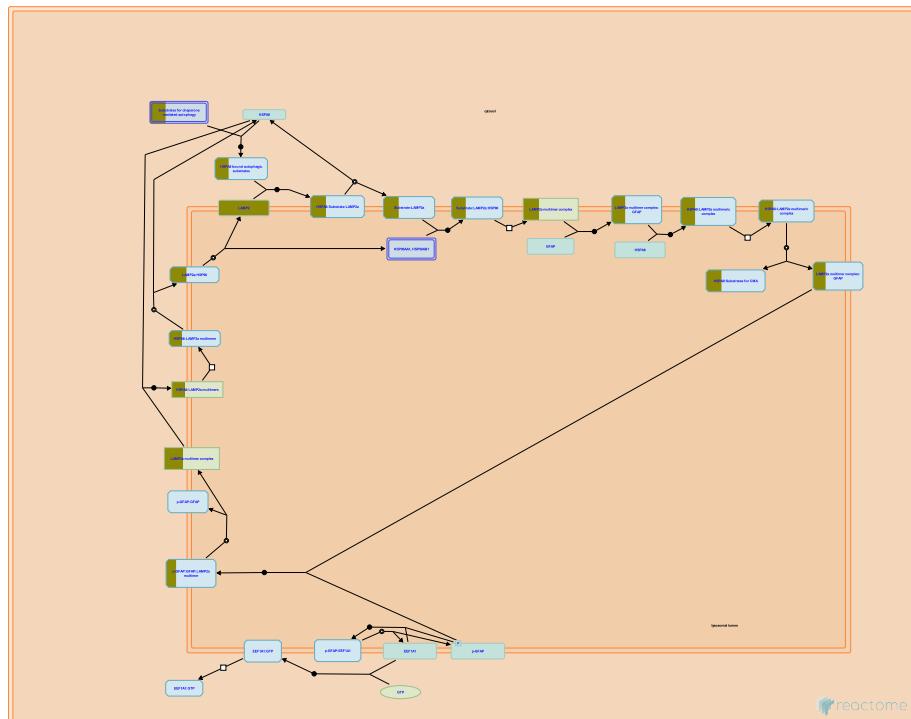
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2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2021-11-26	Modified	Weiser JD

7 submitted entities found in this pathway, mapping to 12 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CAMK2G	Q13555	CRH	P06850	DGCR8	Q8WYQ5

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
MECP2	P51608-1, P51608-2	NCOR1	O75376	PRKACA	P17612
SLC2A3	P11169				
Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
CRH	ENSG00000147571	MECP2	ENST00000303391, ENST00000453960	SLC2A3	ENSG00000059804

4. Chaperone Mediated Autophagy (R-HSA-9613829)



Cellular compartments: lysosomal lumen, cytosol, lysosomal membrane.

In contrary to the vesicle-mediated macroautophagy, the chaperone mediated mechanism of autophagy selectively targets individual proteins to the lysosome for degradation. Chaperones bind intracellular proteins based on recognition motifs and transports them from the cytosol to the lysosomal membrane. Subsequently, the protein is translocated into the lumen for digestion (Cuervo A M et al. 2014, Kaushik S et al. 2018).

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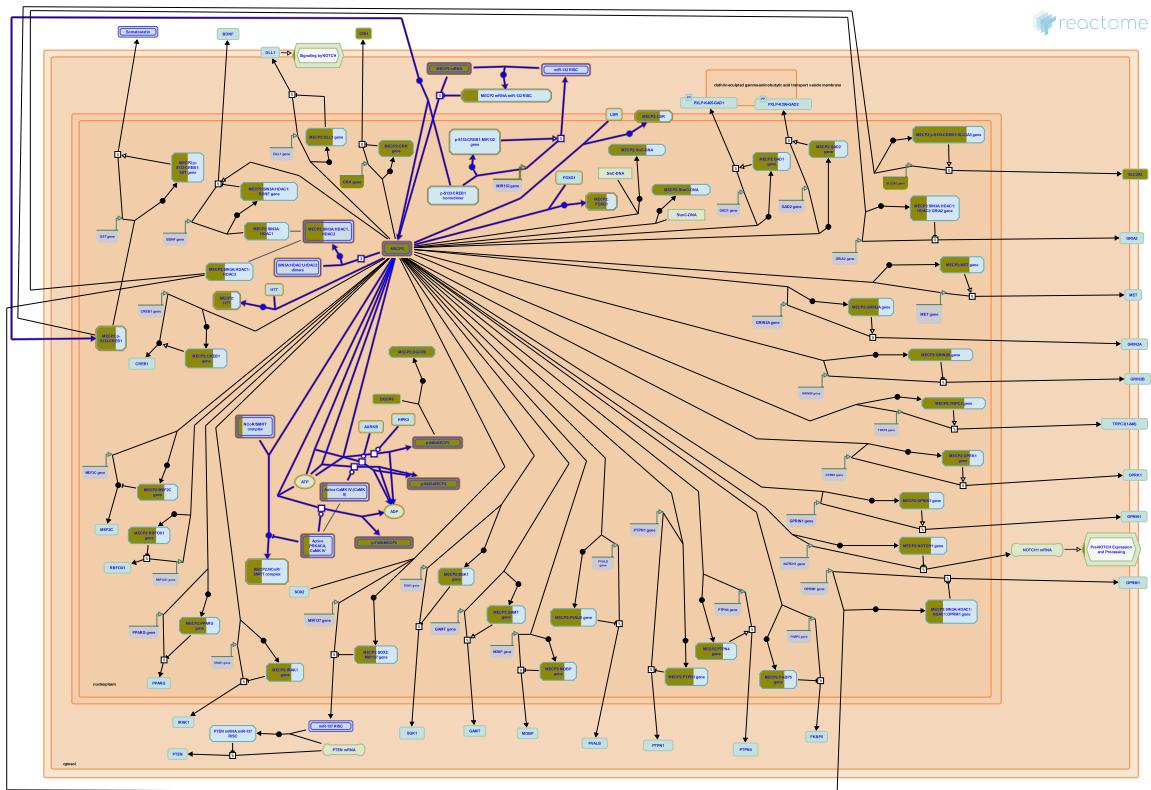
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Date	Action	Author
2018-07-19	Created	Varusai TM
2019-02-21	Authored	Varusai TM
2019-02-22	Reviewed	Metzakopian E
2019-10-31	Revised	Varusai TM
2019-11-08	Edited	Varusai TM
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
ARL13B	Q3SXY8	LAMP1	P13473
PCNT	O95613	UBB	P0CG47, P62979, P62987

5. 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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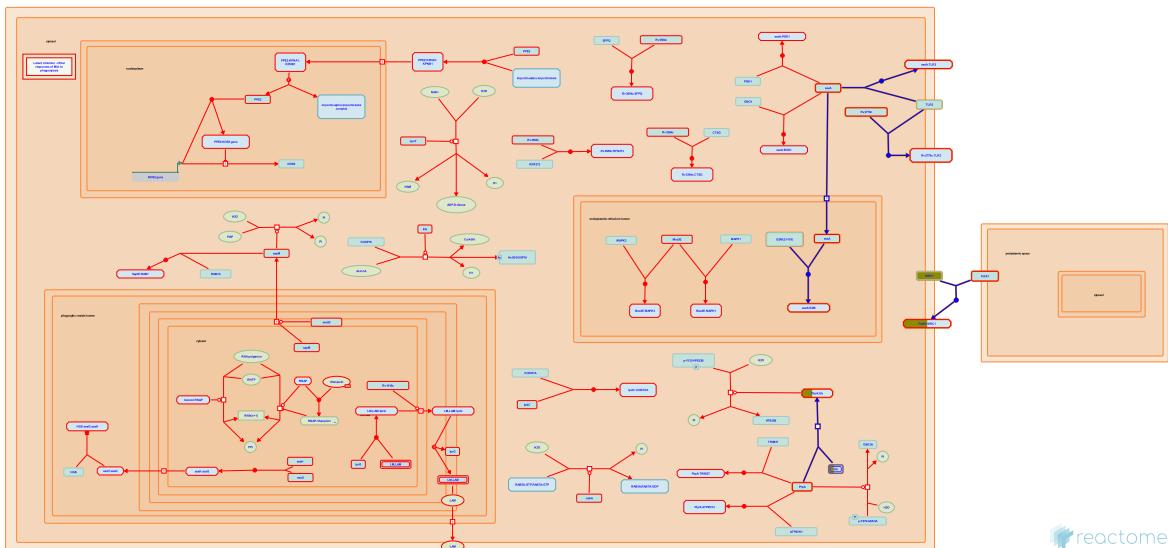
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2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2021-11-26	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
CAMK2G	Q13555	MECP2	P51608-1, P51608-2
NCOR1	O75376	PRKACA	P17612
Input	Ensembl Id		
MECP2	ENST00000303391, ENST00000453960		

6. Modulation by Mtb of host immune system (R-HSA-9637628)



reactome

Diseases: tuberculosis.

Mtb enhances its chances for being taken up by a phagocyte by blocking adaptive immune responses, as well as other innate immune system responses. Components of the bacterial cell wall also specifically promote phagocytosis via both the opsonic pathway and the presentation of adhesins (Esparza et al. 2015).

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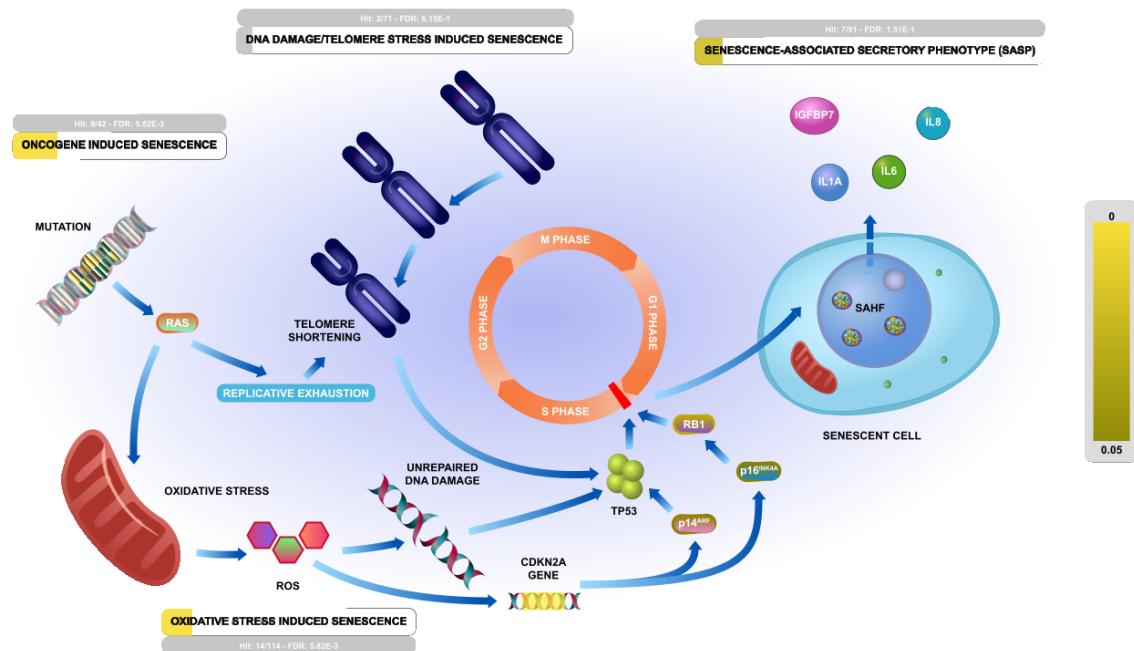
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Date	Action	Author
2019-02-19	Edited	Pardo AM
2019-02-19	Authored	Stephan R
2019-02-19	Created	Pardo AM
2019-10-23	Reviewed	Wilkinson RJ, Deffur A
2019-10-31	Modified	Matthews L

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

Input	UniProt Id	Input	UniProt Id
MRC1	P22897	UBB	P0CG47, P62979, P62987

7. Cellular Senescence (R-HSA-2559583)



Cellular senescence involves irreversible growth arrest accompanied by phenotypic changes such as enlarged morphology, reorganization of chromatin through formation of senescence-associated heterochromatic foci (SAHF), and changes in gene expression that result in secretion of a number of proteins that alter local tissue environment, known as senescence-associated secretory phenotype (SASP).

Senescence is considered to be a cancer protective mechanism and is also involved in aging. Senescent cells accumulate in aged tissues (reviewed by Campisi 1997 and Lopez-Otin 2013), which may be due to an increased senescence rate and/or decrease in the rate of clearance of senescent cells. In a mouse model of accelerated aging, clearance of senescent cells delays the onset of age-related phenotypes (Baker et al. 2011).

Cellular senescence can be triggered by the aberrant activation of oncogenes or loss-of-function of tumor suppressor genes, and this type of senescence is known as the oncogene-induced senescence, with RAS signaling-induced senescence being the best studied. Oxidative stress, which may or may not be caused by oncogenic RAS signaling, can also trigger senescence. Finally, the cellular senescence program can be initiated by DNA damage, which may be caused by reactive oxygen species (ROS) during oxidative stress, and by telomere shortening caused by replicative exhaustion which may be due to oncogenic signaling. The senescent phenotype was first reported by Hayflick and Moorhead in 1961, when they proposed replicative senescence as a mechanism responsible for the cessation of mitotic activity and morphological changes that occur in human somatic diploid cell strains as a consequence of serial passaging, preventing the continuous culture of untransformed cells—the Hayflick limit (Hayflick and Moorhead 1961).

Secreted proteins that constitute the senescence-associated secretory phenotype (SASP), also known as the senescence messaging secretome (SMS), include inflammatory and immune-modulatory cytokines, growth factors, shed cell surface molecules and survival factors. The SASP profile is not significantly affected by the type of senescence trigger or the cell type (Coppe et al. 2008), but the persistent DNA damage may be a deciding SASP initiator (Rodier et al. 2009). SASP components function in an autocrine manner, reinforcing the senescent phenotype (Kuilman et al. 2008, Acosta et al. 2008), and in the paracrine manner, where they may promote epithelial-to-mesenchymal transition (EMT) and malignancy in the nearby premalignant or malignant cells (Coppe et al. 2008).

Senescent cells may remain viable for years, such as senescent melanocytes of moles and nevi, or they can be removed by phagocytic cells. The standard marker for immunohistochemical detection of senescent cells is senescence-associated beta-galactosidase (SA-beta-Gal), a lysosomal enzyme that is not required for senescence.

For reviews of this topic, please refer to Collado et al. 2007, Adams 2009, Kuilman et al. 2010. For a review of differential gene expression between senescent and immortalized cells, please refer to Fridman and Tainsky 2008.

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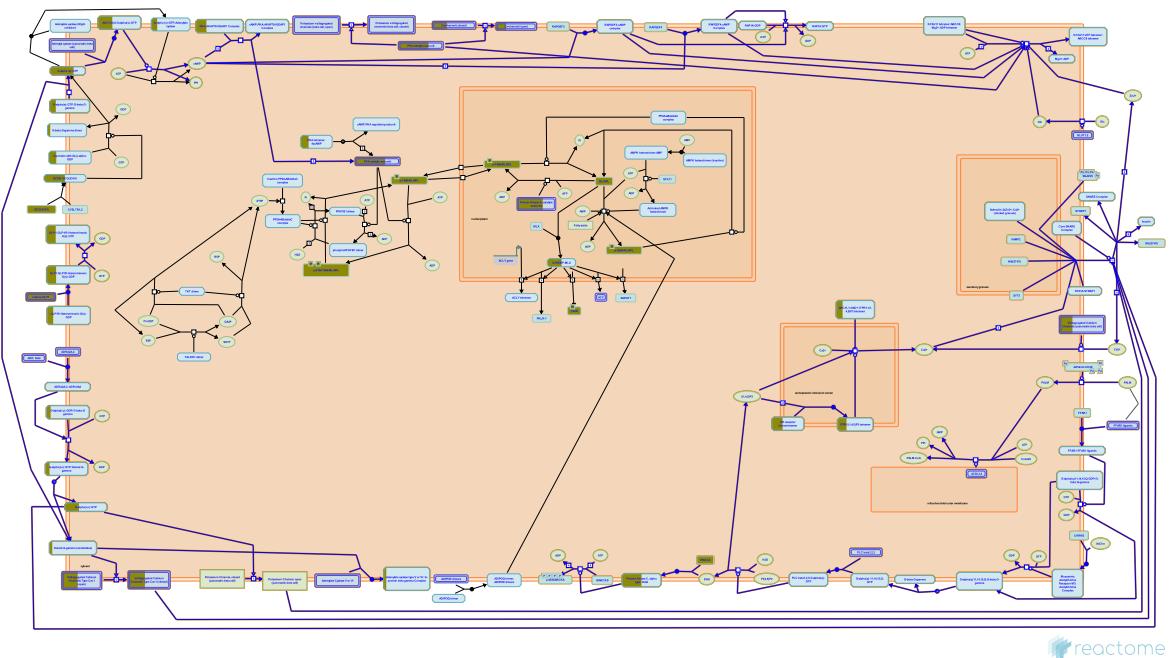
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2013-07-15	Authored	Orlic-Milacic M
2013-09-03	Reviewed	Samarajiwa S
2013-09-30	Revised	Orlic-Milacic M
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CBX6	O95503	CDKN2A	P42771, P42772, Q8N726	EHMT1	Q9H9B1
EP400	Q96L91	HIST1H4E	P62805	MINK1	Q8N4C8
SCMH1	Q96GD3-2	UBB	P0CG47, P62979, P62987		

Input	Ensembl Id	Input	Ensembl Id
CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755	MINK1	ENSG00000141503

8. Regulation of insulin secretion (R-HSA-422356)



Cellular compartments: secretory granule membrane, endoplasmic reticulum membrane, plasma membrane, nucleoplasm, extracellular region, endoplasmic reticulum lumen, mitochondrial matrix, cytosol, secretory granule lumen.

Pancreatic beta cells integrate signals from several metabolites and hormones to control the secretion of insulin. In general, glucose triggers insulin secretion while other factors can amplify or inhibit the amount of insulin secreted in response to glucose. Factors which increase insulin secretion include the incretin hormones Glucose-dependent insulinotropic polypeptide (GIP and glucagon-like peptide-1 (GLP-1), acetylcholine, and fatty acids. Factors which inhibit insulin secretion include adrenaline and noradrenaline.

Increased blood glucose levels from dietary carbohydrate play a dominant role in insulin release from the beta cells of the pancreas. Glucose catabolism in the beta cell is the transducer that links increased glucose levels to insulin release. Glucose uptake and glycolysis generate cytosolic pyruvate; pyruvate is transported to mitochondria and converted both to oxaloacetate which increases levels of TCA cycle intermediates, and to acetyl-CoA which is oxidized to CO₂ via the TCA cycle. The rates of ATP synthesis and transport to the cytosol increase, plasma membrane ATP-sensitive inward rectifying potassium channels (KATP channels) close, the membrane depolarizes, and voltage-gated calcium channels in the membrane open (Muio and Newgard 2008; Wiederkehr and Wollheim 2006).

Elevated calcium concentrations near the plasma membrane cause insulin secretion in two phases: an initial high rate within minutes of glucose stimulation and a slow, sustained release lasting longer than 30 minutes. In the initial phase, 50-100 insulin granules already docked at the membrane are exocytosed. Exocytosis is rendered calcium-dependent by Synaptotagmin V/IX, a calcium-binding membrane protein located in the membrane of the docked granule, although the exact action of Synaptotagmin in response to calcium is unknown. Calcium also causes a translocation of reserve granules within the cell towards the plasma membrane for release in the second, sustained phase of secretion. Human cells contain L-type (continually reopening), P/Q-type (long burst), R-type (long burst), and T-type (short burst) calcium channels and these partly account for differences between the two phases of secretion. Other factors that distinguish the two phases are not yet fully known (Bratanova-Tochkova et al. 2002; Henquin 2000; MacDonald et al. 2005).

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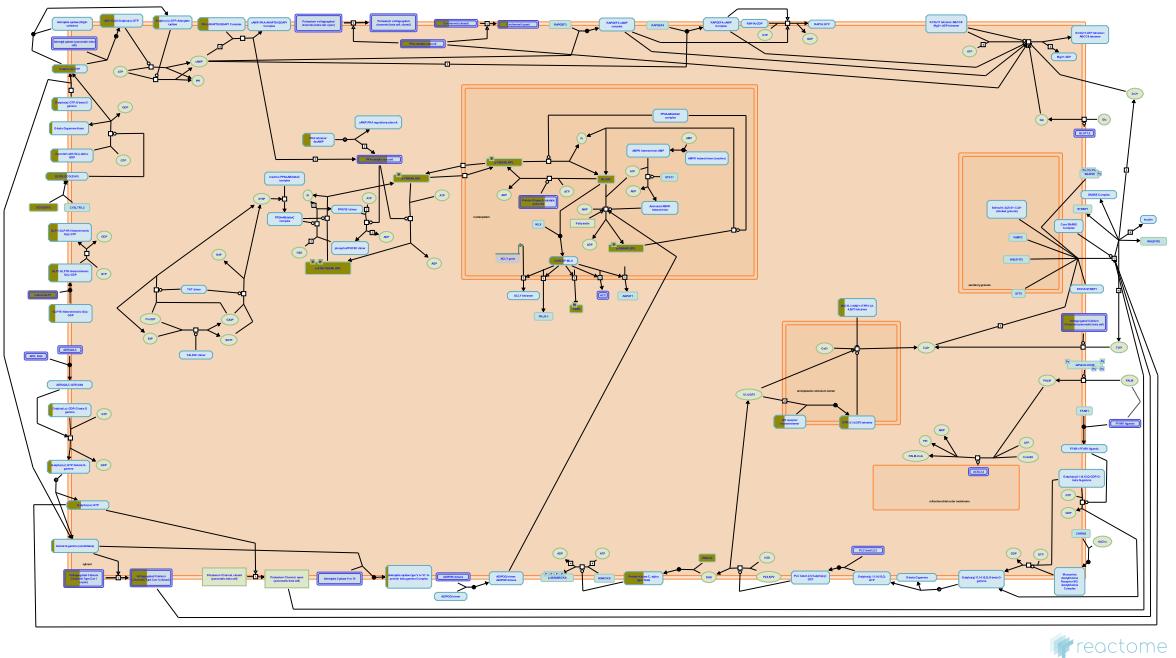
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2009-05-28	Created	May B
2009-09-07	Reviewed	D'Eustachio P
2021-11-28	Modified	Weiser JD

8 submitted entities found in this pathway, mapping to 11 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CACNA2D2	Q9NY47	CACNB2	Q08289	GCG	P01275
GNAI2	P04899	GNAS	P63092, Q5JWF2	GNB2	P62879
ITPR1	Q14643	PRKACA	P17252, P17612, P22612		

9. Integration of energy metabolism (R-HSA-163685)



Cellular compartments: cytosol.

Many hormones that affect individual physiological processes including the regulation of appetite, absorption, transport, and oxidation of foodstuffs influence energy metabolism pathways. While **insulin** mediates the storage of excess nutrients, **glucagon** is involved in the mobilization of energy resources in response to low blood glucose levels, principally by stimulating hepatic glucose output. Small doses of glucagon are sufficient to induce significant glucose elevations. These hormone-driven regulatory pathways enable the body to sense and respond to changed amounts of nutrients in the blood and demands for energy.

Glucagon and Insulin act through various metabolites and enzymes that target specific steps in metabolic pathways for sugar and fatty acids. The processes responsible for the long-term control of fat synthesis and short term control of glycolysis by key metabolic products and enzymes are annotated in this module as six specific pathways:

Pathway 1. Glucagon signalling in metabolic pathways: In response to low blood glucose, pancreatic alpha-cells release glucagon. The binding of glucagon to its receptor results in increased cAMP synthesis, and Protein Kinase A (PKA) activation.

Pathway 2. PKA mediated phosphorylation: PKA phosphorylates key enzymes, e.g., 6-Phosphofructo-2-kinase /Fructose-2,6-bisphosphatase (PF2K-Pase) at serine 36, and regulatory proteins, e.g., Carbohydrate Response Element Binding Protein (ChREBP) at serine 196 and threonine 666.

In brief, the binding of insulin to its receptor leads to increased protein phosphatase activity and to hydrolysis of cAMP by cAMP phosphodiesterase. These events counteract the regulatory effects of glucagon.

Pathway 3: Insulin stimulates increased synthesis of Xylulose-5-phosphate (Xy-5-P). Activation of the insulin receptor results indirectly in increased Xy-5-P synthesis from Glyceraldehyde-3-phosphate and Fructose-6-phosphate. Xy-5-P, a metabolite of the pentose phosphate pathway, stimulates protein phosphatase PP2A.

Pathway 4: AMP Kinase (AMPK) mediated response to high AMP:ATP ratio: In response to diet with high fat content or low energy levels, the cytosolic AMP:ATP ratio is increased. AMP triggers a complicated cascade of events. In this module we have annotated only the phosphorylation of ChREBP by AMPK at serine 568, which inactivates this transcription factor.

Pathway 5: Dephosphorylation of key metabolic factors by PP2A: Xy-5-P activated PP2A efficiently dephosphorylates phosphorylated PF2K-Pase resulting in the higher output of F-2,6-P2 that enhances PFK activity in the glycolytic pathway. PP2A also dephosphorylates (and thus activates) cytosolic and nuclear ChREBP.

Pathway 6: Transcriptional activation of metabolic genes by ChREBP: Dephosphorylated ChREBP activates the transcription of genes involved in glucose metabolism such as pyruvate kinase, and lipogenic genes such as acetyl-CoA carboxylase, fatty acid synthetase, acyl CoA synthase and glycerol phosphate acyl transferase.

The illustration below summarizes this network of events. Black lines are metabolic reactions, red lines are negative regulatory events, and green lines are positive regulatory events (figure reused with permission from Veech (2003) - Copyright (2003) National Academy of Sciences, U.S.A.).

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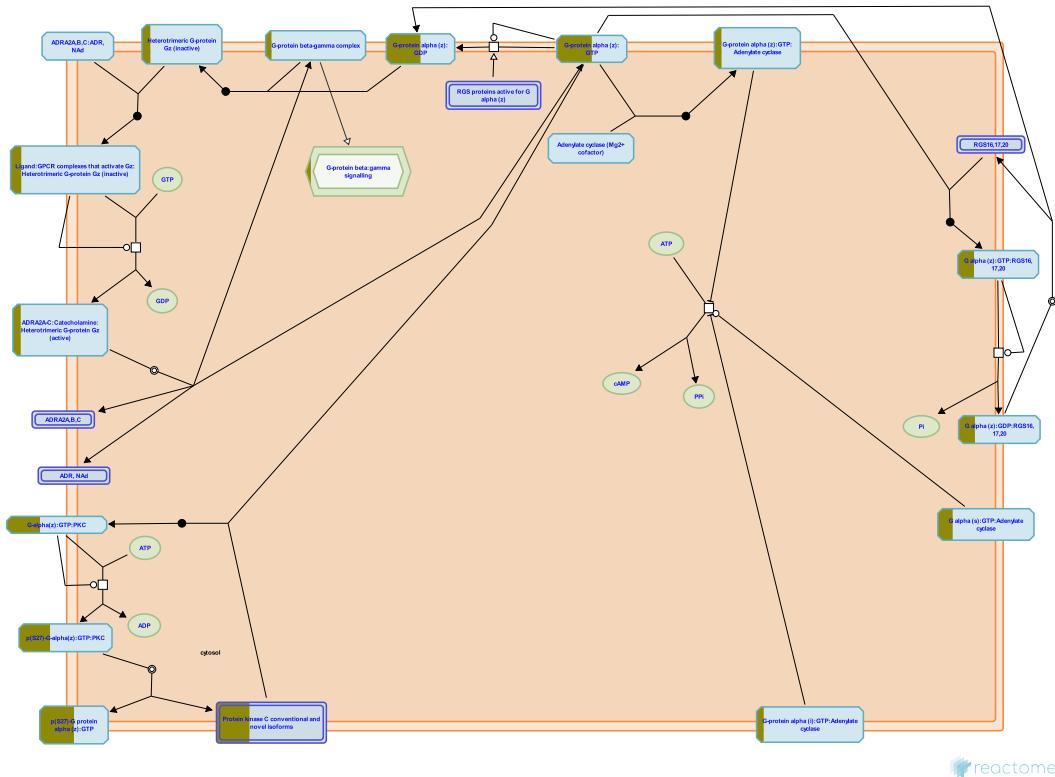
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2005-05-11	Created	Gopinathrao G, D'Eustachio P
2005-09-10	Reviewed	Rush MG
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CACNA2D2	Q9NY47	CACNB2	Q08289	FASN	P49327
GCG	P01275	GNAI2	P04899	GNAS	P63092, Q5JWF2
GNB2	P62879	ITPR1	Q14643	MLXIPL	Q9NP71
PRKACA	P17252, P17612, P22612				

10. G alpha (z) signalling events (R-HSA-418597)



Cellular compartments: plasma membrane.

The heterotrimeric G protein G alpha (z), is a member of the G (i) family. Unlike other G alpha (i) family members it lacks an ADP ribosylation site cysteine four residues from the carboxyl terminus and is thus pertussis toxin-insensitive. It inhibits adenylyl cyclase types I, V and VI (Wong Y H et al. 1992). G alpha (z) interacts with the Rap1 GTPase activating protein (Rap1GAP) to attenuate Rap1 signaling. Like all G-proteins G alpha (z) has an intrinsic GTPase activity, but this activity tends to be lower for the pertussis toxin insensitive G-proteins, most strikingly so for G alpha (z), whose kcat value for GTP hydrolysis is 200-fold lower than those of G alpha (s) or G alpha (i) (Graziano et al. 1989). G alpha (z) knockout mice have disrupted platelet aggregation at physiological concentrations of epinephrine and responses to several neuroactive drugs are altered (Yang et al. 2000). Regulator of G-protein Signalling (RGS) proteins can regulate the activity of G alpha (z) (Soundararajan M et al. 2008).

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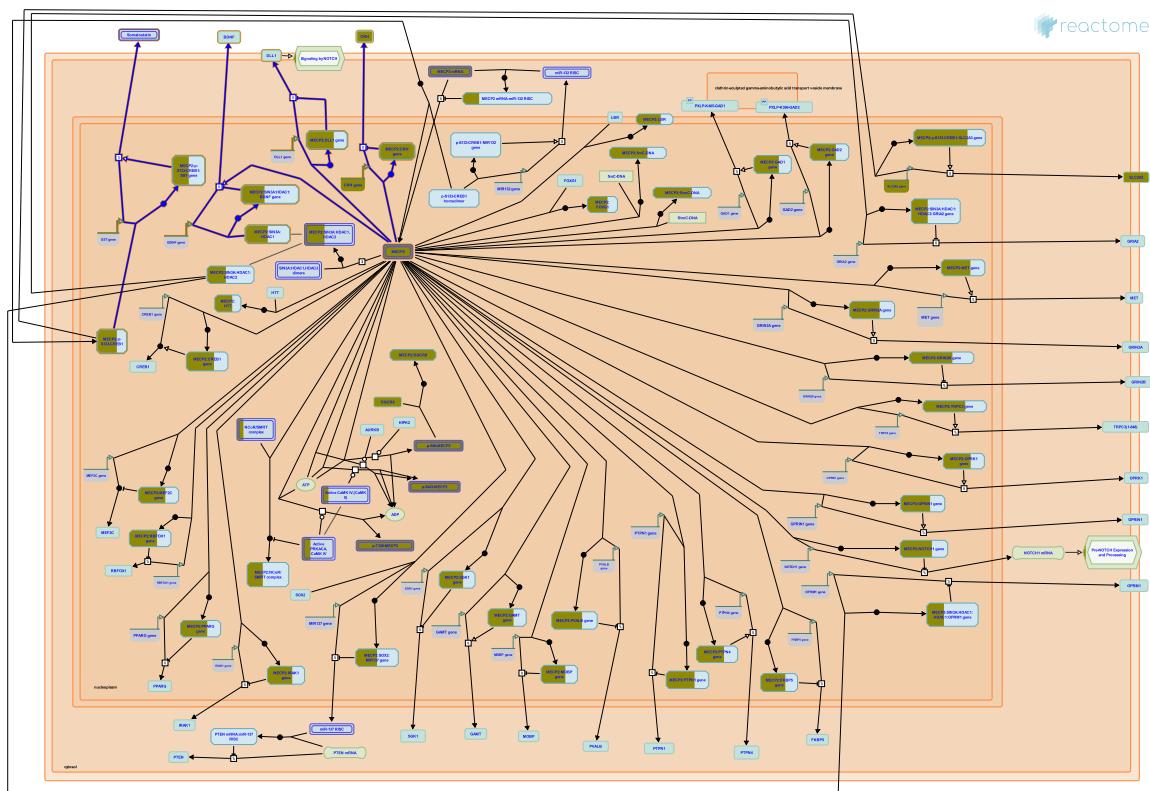
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2009-04-24	Created	Jupe S

Date	Action	Author
2009-06-03	Reviewed	Akkerman JW
2009-09-09	Edited	Jupe S
2017-07-10	Revised	Varusai TM
2021-11-27	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
GNAI2	P04899	GNAS	P63092, Q5JWF2	GNAZ	P19086
GNB2	P62879	PCK1	P05771	PRKACA	P17252
PRKCE	Q02156				

11. 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

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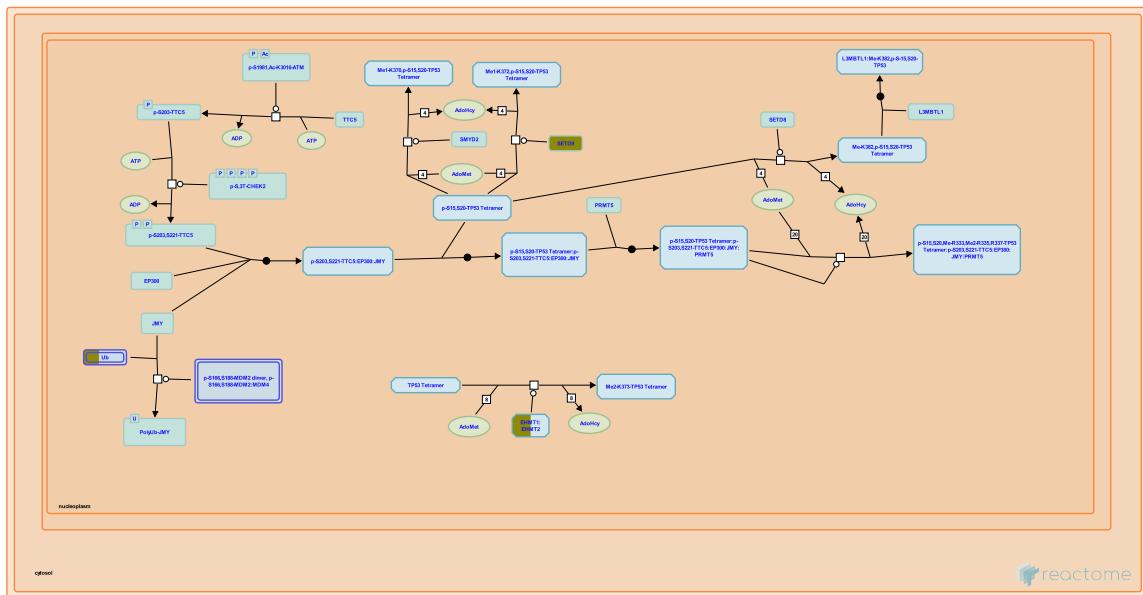
Date	Action	Author
2017-09-25	Created	Orlic-Milacic M

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

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

Input	UniProt Id	Input	UniProt Id
CRH	P06850	MECP2	P51608-1, P51608-2
Input	Ensembl Id		
CRH	ENSG00000147571		

12. Regulation of TP53 Activity through Methylation (R-HSA-6804760)



TP53 (p53) undergoes methylation on several lysine and arginine residues, which modulates its transcriptional activity.

PRMT5, recruited to TP53 as part of the ATM-activated complex that includes TTC5, JMY and EP300 (p300), methylates TP53 arginine residues R333, R335 and R337. PRMT5-mediated methylation promotes TP53-stimulated expression of cell cycle arrest genes (Shikama et al. 1999, Demonacos et al. 2001, Demonacos et al. 2004, Adams et al. 2008, Adams et al. 2012). SETD9 (SET9) methylates TP53 at lysine residue K372, resulting in increased stability and activity of TP53 (Chuikov et al. 2004, Couture et al. 2006, Bai et al. 2011).

TP53 transcriptional activity is repressed by SMYD2-mediated methylation of TP53 at lysine residue K370 (Huang et al. 2006). Dimethylation of TP53 at lysine residue K373 by the complex of methyl-transferases EHMT1 and EHMT2 also represses TP53-mediated transcription (Huang et al. 2010). The chromatin compaction factor L3MBTL1 binds TP53 monomethylated at lysine K382 by SETD8 (SET8) and, probably through changing local chromatin architecture, represses transcription of TP53 targets (West et al. 2010). The histone lysine-specific demethylase LSD1 interacts with TP53 and represses p53-mediated transcriptional activation (Huang et al. 2007). PRMT1 and CARM1 can also modulate p53 functions in a cooperative manner (An et al. 2004).

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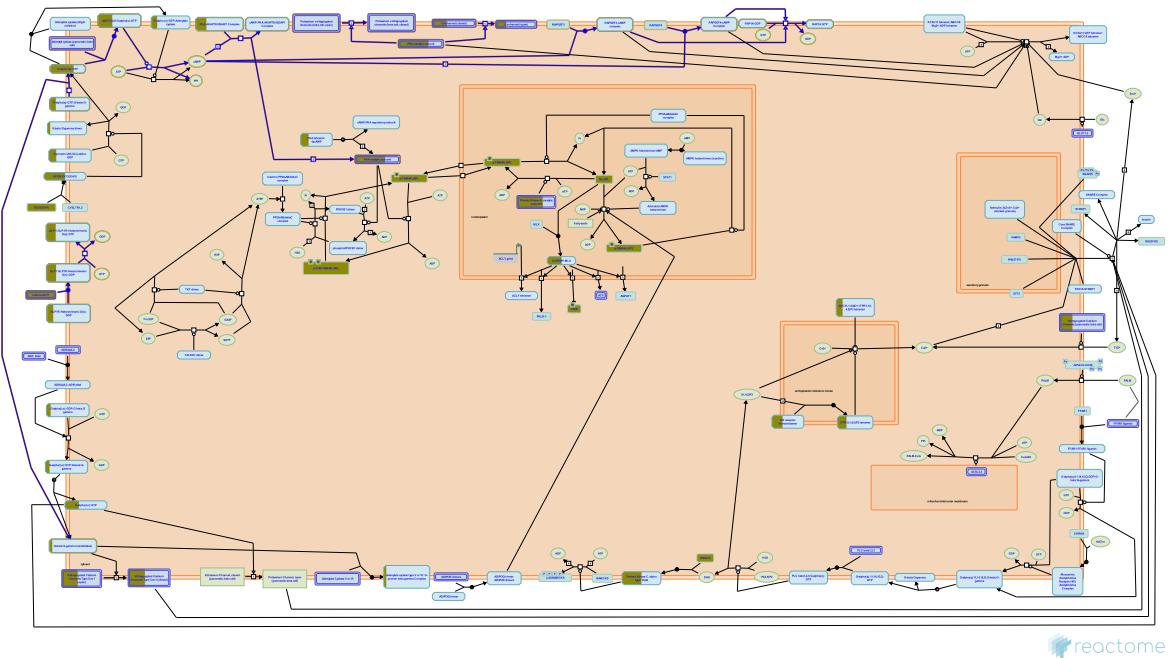
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Date	Action	Author
2015-10-14	Edited	Orlic-Milacic M
2015-10-14	Authored	Orlic-Milacic M
2015-10-14	Created	Orlic-Milacic M
2016-02-04	Reviewed	Zaccara S, Inga A
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
EHMT1	Q9H9B1	SETD9	Q8NE22	UBB	P0CG47, P62979, P62987

13. Glucagon-like Peptide-1 (GLP1) regulates insulin secretion (R-HSA-381676)



Cellular compartments: plasma membrane, cytosol.

Glucagon-like Peptide-1 (GLP-1) is secreted by L-cells in the intestine in response to glucose and fatty acids. GLP-1 circulates to the beta cells of the pancreas where it binds a G-protein coupled receptor, GLP-1R, on the plasma membrane. The binding activates the heterotrimeric G-protein G(s), causing the alpha subunit of G(s) to exchange GDP for GTP and dissociate from the beta and gamma subunits.

The activated G(s) alpha subunit interacts with Adenylyl Cyclase VIII (Adenylate Cyclase VIII, AC VIII) and activates AC VIII to produce cyclic AMP (cAMP). cAMP then has two effects: 1) cAMP activates Protein Kinase A (PKA), and 2) cAMP activates Epac1 and Epac2, two guanyl nucleotide exchange factors.

Binding of cAMP to PKA causes the catalytic subunits of PKA to dissociate from the regulatory subunits and become an active kinase. PKA is known to enhance insulin secretion by closing ATP-sensitive potassium channels, closing voltage-gated potassium channels, releasing calcium from the endoplasmic reticulum, and affecting insulin secretory granules. The exact mechanisms for PKA's action are not fully known. After prolonged increases in cAMP, PKA translocates to the nucleus where it regulates the PDX-1 and CREB transcription factors, activating transcription of the insulin gene.

cAMP produced by AC VIII also activates Epac1 and Epac2, which catalyze the exchange of GTP for GDP on G-proteins, notably Rap1A.. Rap1A regulates insulin secretory granules and is believed to activate the Raf/MEK/ERK mitogenic pathway leading to proliferation of beta cells. The Epac proteins also interact with RYR calcium channels on the endoplasmic reticulum, the SUR1 subunits of ATP-sensitive potassium channels, and the Piccolo:Rim2 calcium sensor at the plasma membrane.

References

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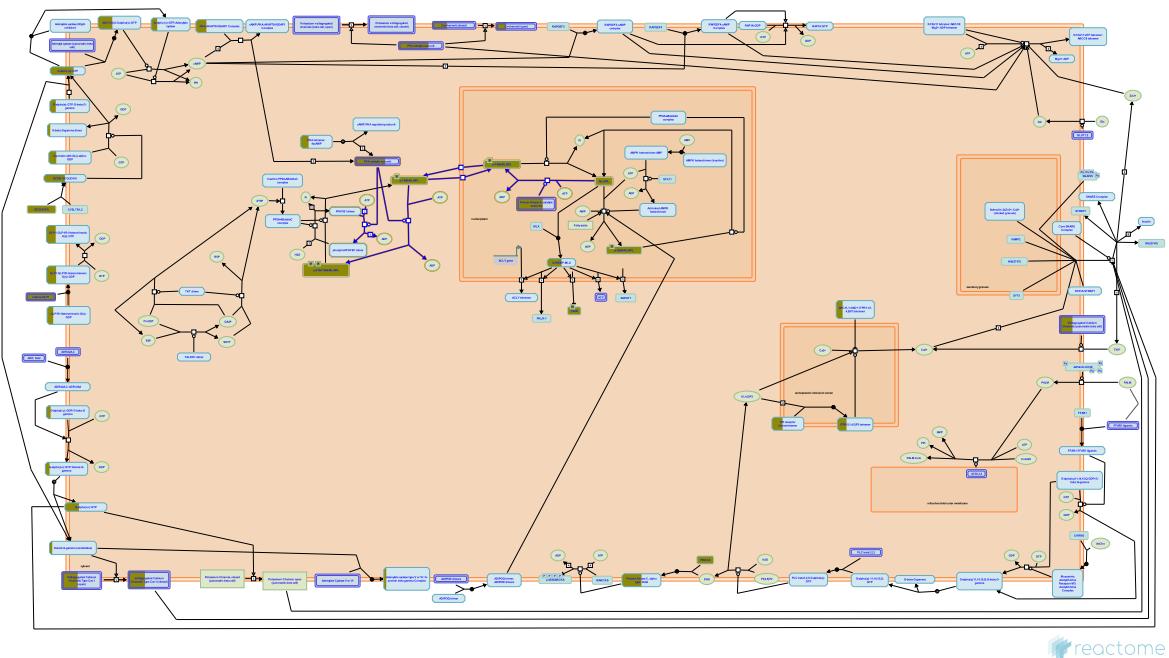
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Date	Action	Author
2008-11-20	Created	May B
2009-05-28	Edited	May B
2009-05-28	Authored	May B
2009-06-02	Reviewed	Gillespie ME
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
GCG	P01275	GNAS	P63092, Q5JWF2	GNB2	P62879
ITPR1	Q14643	PRKACA	P17612, P22612		

14. PKA-mediated phosphorylation of key metabolic factors (R-HSA-163358)



Cellular compartments: nucleoplasm, cytosol.

Upon dissociation of protein kinase A (PKA) tetramers in the presence of cAMP, the released PKA catalytic monomers phosphorylate specific serine and threonine residues of several metabolic enzymes. These target enzymes include glycogen phosphorylase kinase, glycogen synthase and PF2K-Pase. PKA also phosphorylates ChREBP (Carbohydrate Response Element Binding Protein), preventing its movement into the nucleus and thus its function as a positive transcription factor for genes involved in glycolytic and lipogenic reactions.

References

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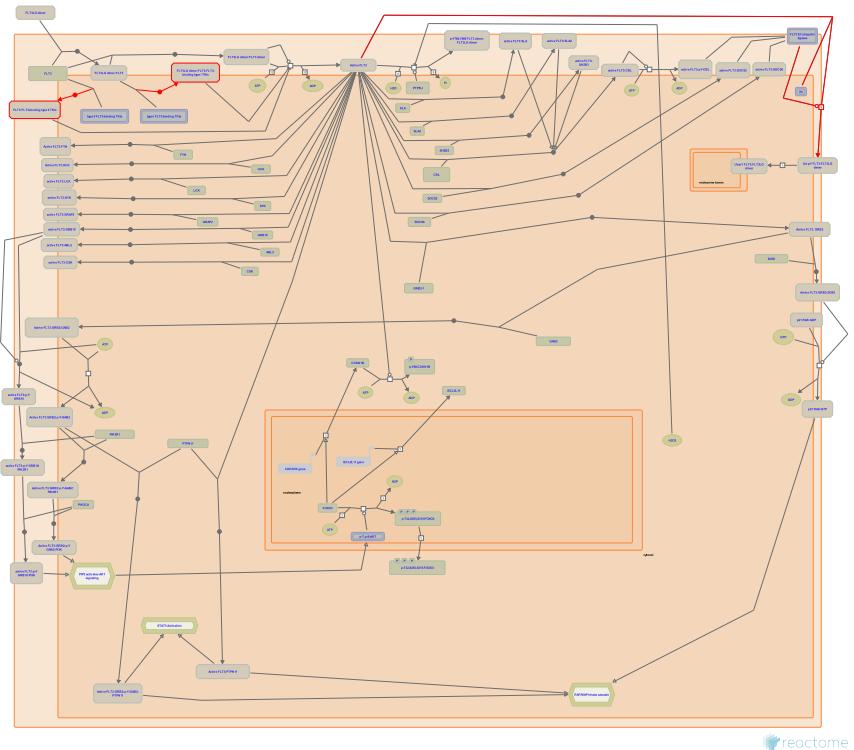
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Date	Action	Author
2005-04-28	Created	Gopinathrao G
2005-05-13	Authored	Gopinathrao G
2021-11-27	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
MLXIPL	Q9NP71	PRKACA	P17612, P22612

15. FLT3 signaling by CBL mutants (R-HSA-9706377)



Diseases: cancer.

Missense and splicing mutants have been identified in the E3 ubiquitin ligase CBL in a number of cancers including acute and chronic myeloid leukemias, among others. These cancers show elevated signaling through FLT3 as a result of impaired CBL-mediated downregulation of the receptor (Sargin et al, 2007; Reindl et al, 2009; Caligiuri et al, 2007; Abbas et al, 2008).

References

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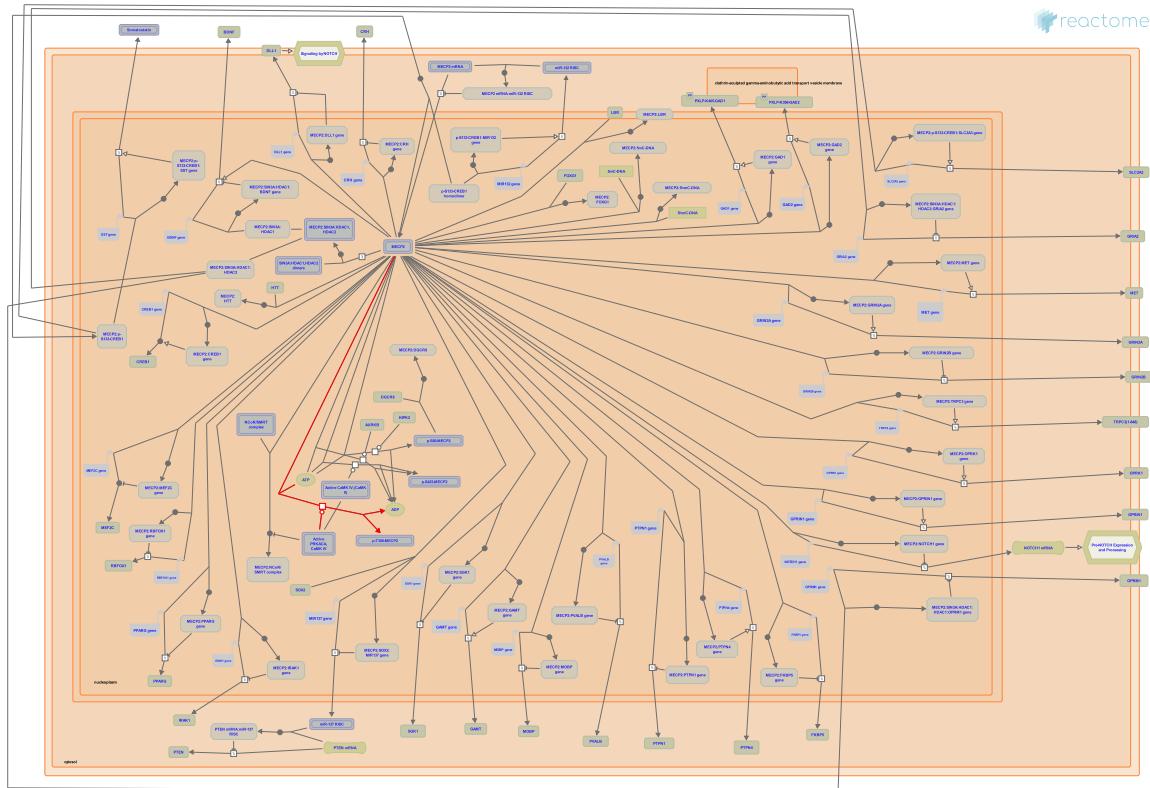
Date	Action	Author
2020-11-04	Created	Rothfels K
2020-11-06	Modified	Rothfels K

Date	Action	Author
2020-11-06	Edited	Rothfels K
2020-11-06	Reviewed	Kazi JU
2020-11-06	Authored	Rothfels K

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

16. Loss of phosphorylation of MECP2 at T308 (R-HSA-9022535)



Cellular compartments: nucleoplasm.

Diseases: Rett syndrome.

Missense mutations of methyl-CpG-binding protein 2 (MECP2) in the vicinity of its threonine T308 phosphorylation site can negatively affect the ability of MECP2 to be phosphorylated at T308 in response to neuronal membrane depolarization (neuronal activity) (Ebert et al. 2013).

References

Kastan NR, Greenberg ME, Ekiert R, Bird AP, Lyst MJ, Hu LS, ... Robinson ND (2013). Activity-dependent phosphorylation of MeCP2 threonine 308 regulates interaction with NCoR. *Nature*, 499, 341-5. [\[CrossRef\]](#)

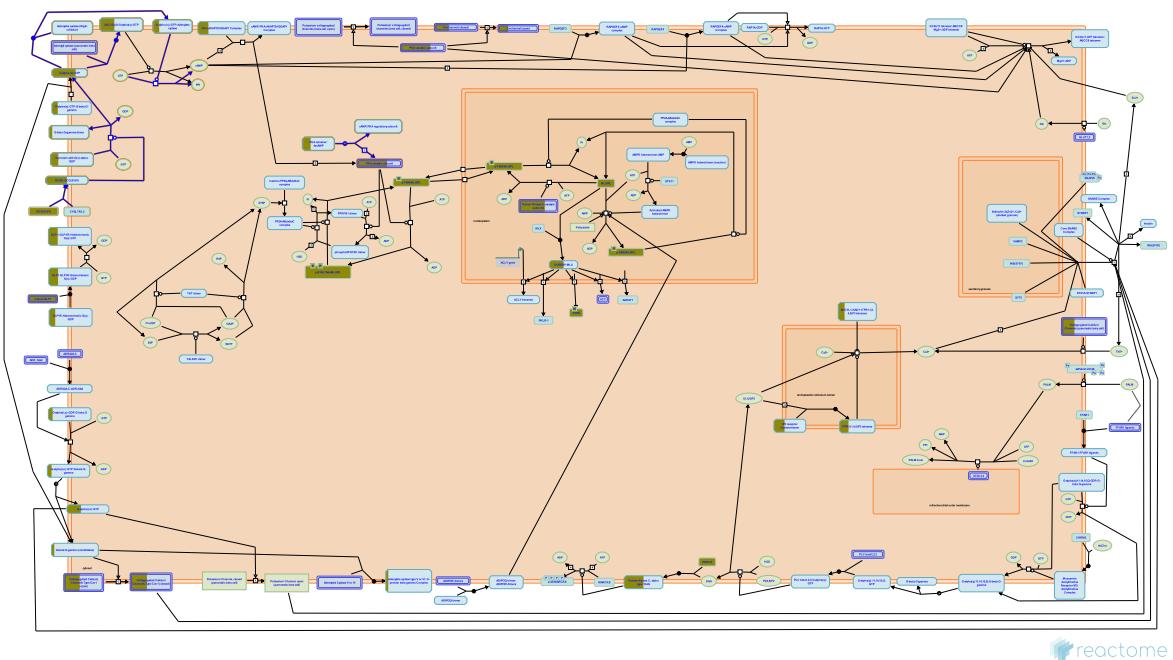
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Date	Action	Author
2017-09-25	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
MECP2	P51608-1, P51608-2	PRKACA	P17612

17. Glucagon signaling in metabolic regulation (R-HSA-163359)



Glucagon and insulin are peptide hormones released from the pancreas into the blood, that normally act in complementary fashion to stabilize blood glucose concentration. When blood glucose levels rise, insulin release stimulates glucose uptake from the blood, glucose breakdown (glycolysis), and glucose storage as glycogen. When blood glucose levels fall, glucagon release stimulates glycogen breakdown and de novo glucose synthesis (gluconeogenesis), while inhibiting glycolysis and glycogen synthesis.

At a molecular level, the binding of glucagon to the extracellular face of its receptor causes conformational changes in the receptor that allow the dissociation and activation of subunits Gs and Gq. The activation of Gq leads to the activation of phospholipase C, production of inositol 1,4,5-triphosphate, and subsequent release of intracellular calcium. The activation of Gs leads to activation of adenylate cyclase, an increase in intracellular cAMP levels, and activation of protein kinase A (PKA). Active PKA phosphorylates key enzymes of glycogenolysis, glycogenesis, gluconeogenesis, and glycolysis, modifying their activities. These signal transduction events, and some of their downstream consequences, are illustrated below (adapted from Jiang and Zhang, 2003).

References

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Edit history

Date	Action	Author
2005-04-28	Authored	Gopinathrao G
2005-04-28	Created	Gopinathrao G
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
GCG	P01275	GNAS	P63092, Q5JWF2
GNB2	P62879	PRKACA	P17612, P22612

18. Loss of function of MECP2 in Rett syndrome ([R-HSA-9005891](#))



Diseases: Rett syndrome.

Loss of function mutations in methyl-CpG-binding protein 2 (MECP2), an epigenetic regulator of transcription, are the major cause of Rett syndrome, a neurodevelopmental disorder that affects 1 in 10,000-15,000 female births. The symptoms of Rett syndrome appear after 6-18 months of apparently normal postnatal development and include regression of acquired language and motor skills, stereotypic hand movements, intellectual disability, epileptic seizures and respiratory disturbances. Besides Rett syndrome, aberrant MECP2 expression is implicated as an underlying cause of other neuropsychiatric disorders (reviewed by Banerjee et al. 2012, Ebert and Greenberg 2013, Lyst and Bird 2015). Only functionally characterized MECP2 mutations are annotated. For a comprehensive list of MECP2 mutations reported in Rett syndrome, please refer to the RettBASE (<http://mecp2.chw.edu.au>), a database dedicated to curation of disease variants of MECP2, CDKL5 and FOXG1 in Rett syndrome (Krishnaraj et al. 2017).

References

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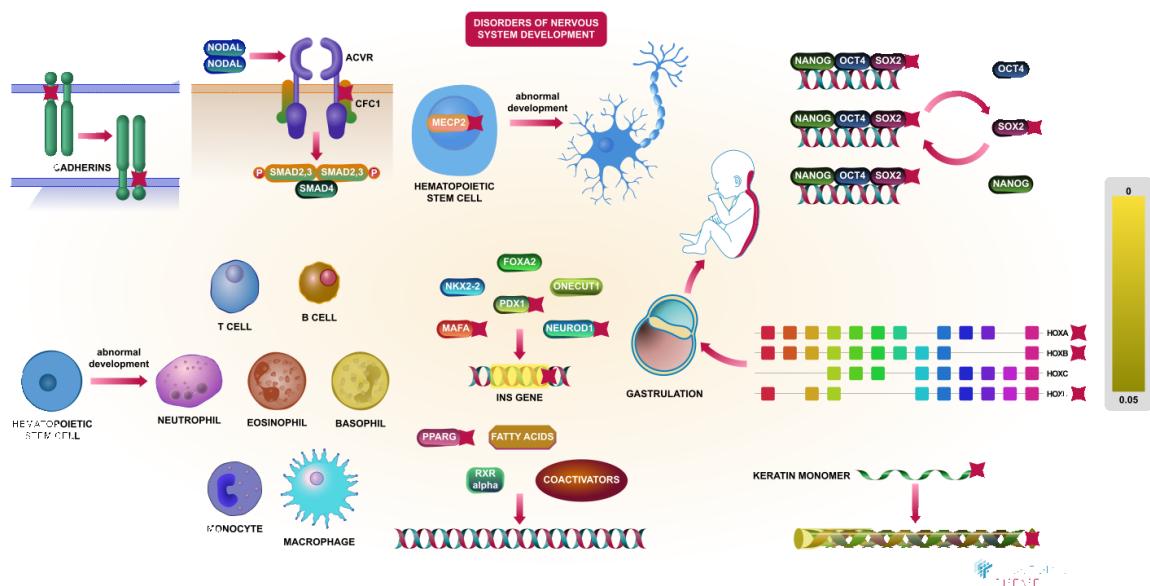
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Date	Action	Author
2017-05-11	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Edited	Orlic-Milacic M
2018-09-05	Modified	Shorser S

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
MECP2	P51608-1, P51608-2	NCOR1	O75376	PRKACA	P17612

19. Disorders of Developmental Biology (R-HSA-9675151)



Developmental disorders affect formation of body organs and organ systems. The causes of defects in human development are diverse and incompletely understood, and include environmental insults such as nutrient deficiency, exposure to toxins and infections (Gilbert 2000, National Research Council (US) Committee on Developmental Toxicology 2000, Taylor and Rogers 2005, Zilbauer et al. 2016, Izvolskaia et al. 2018), as well as genetic causes such as aneuploidy and other chromosomal abnormalities, and germline mutations in genes that regulate normal development. It is estimated that about 40% of human developmental disabilities can be attributed to genetic aberrations (Sun et al. 2015), of which at least 25% are due to mutations affecting single genes (Chong et al. 2015), and this latter group of Mendelian developmental disorders is the focus of curation in Reactome.

Disorders of nervous system development affect the function of the central nervous system (CNS) and impair motor skills, cognition, communication and/or behavior (reviewed by Ismail and Shapiro 2019). So far, we have annotated the role of loss-of-function mutations in methyl-CpG-binding protein 2 (MECP2), an epigenetic regulator of transcription, in Rett syndrome, a pervasive developmental disorder (Pickett and London 2005, Ferreri 2014).

Disorders of myogenesis are rare hereditary muscle diseases that in the case of congenital myopathies are defined by architectural abnormalities in the muscle fibres (Pelin and Wallgren-Pettersson 2019, Phadke 2019, Radke et al. 2019, Claeys 2020) and in the case of muscular dystrophies by increased muscle breakdown that progresses with age (Pasrija and Tadi 2020). Mutations in cadherin family genes are present in some types of muscular dystrophy (Puppo et al. 2015).

Disorders of pancreas development result in pancreatic agenesis, where a critical mass of pancreatic tissue is congenitally absent. For example, the PDX1 gene is a master regulator of beta cell differentiation and homozygous deletions or inactivating mutations in PDX1 gene cause whole pancreas agenesis. PDX1 gene haploinsufficiency impairs glucose tolerance and leads to development of diabetes mellitus (Hui and Perfetti 2002, Babu et al. 2007, Chen et al. 2008).

Left-right asymmetry disorders are caused by mutations in genes that regulate the characteristic asymmetry of internal organs in vertebrates. Normally, cardiac apex, stomach and spleen are positioned towards the left side, while the liver and gallbladder are on the right. Loss-of-function mutations in the CFC1 gene, whose protein product functions as a co-factor in Nodal signaling, result in heterotaxic phenotype in affected patients, manifested by randomized organ positioning (Bamford et al. 2000).

Congenital lipodystrophies are characterized by a lack of adipose tissue, which predisposes affected patient to development of insulin resistance and related metabolic disorders. The severity of metabolic complications is correlates with the extent of adipose tissue loss. Loss-of-function mutations in the PPARG gene, encoding a key transcriptional regulator of adipocyte development and function, are a well-established cause of familial partial lipodystrophy type 3 (FPLD3) (Broekema et al. 2019).

Congenital stem cell disorders are caused by mutations in genes that regulate the balance between stem cells maintenance and commitment to differentiated lineages. Loss-of-function mutations in the SOX2 gene, which encodes a transcription factor involved in the maintenance of totipotency during embryonic preimplantation period, pluripotency of embryonic stem cells, and multipotency of neural stem cells, are the cause of anophthalmia (the absence of an eye) and microphthalmia (the presence of a small eye within the orbit) (Verma and Fitzpatrick 2007, Sarlak and Vincent 2016).

HOX-related structural birth defects are caused by loss-of-function mutations in HOX family genes. HOX transcription factors play a fundamental role in body patterning during embryonic development, and HOX mutation are an underlying cause of many congenital limb malformations (Goodman 2002).

Congenital keratinization disorders are caused by dominant negative mutation in keratin genes and depending on where the affected keratin gene is expressed, they affect epithelial tissues such as skin, cornea, hair and/or nails (McLean and Moore 2011).

Disorders of immune system development are caused by mutations in genes that regulate differentiation of blood cell lineages involved in immune defense, leading to immune system defects. For example, mutations in the gene encoding CSF3R, a receptor for the granulocyte-colony stimulating factor, result in congenital neutropenia, characterized by a maturation arrest of granulopoiesis at the level of promyelocytes. Patients with severe congenital neutropenia are prone to recurrent, often life-threatening infections from an early age and may be predisposed to myelodysplastic syndromes or acute myeloid leukemia (Germeshausen et al. 2008; Skokowa et al. 2017).

References

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Edit history

Date	Action	Author
2020-01-31	Created	Orlic-Milacic M
2020-02-21	Authored	Orlic-Milacic M
2020-02-24	Edited	Orlic-Milacic M
2020-02-24	Reviewed	D'Eustachio P
2020-08-18	Reviewed	D'Eustachio P
2020-08-24	Edited	Orlic-Milacic M
2020-08-25	Modified	Matthews L

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
MECP2	P51608-1, P51608-2	NCOR1	O75376	PRKACA	P17612

20. Pervasive developmental disorders ([R-HSA-9005895](#))

Loss of function of MECP2
in Rett syndrome



Diseases: pervasive developmental disorder.

Pervasive developmental disorders (PDDs) largely overlap with the autism spectrum disorders (ASDs). PDDs manifest in childhood and mainly affect social interaction, including communication and behavior. PDDs can be caused by mutations in genes involved in brain development and function, environmental insults, or the combination of environmental factors and genetic susceptibility. For review of this topic, please refer to Pickett and London 2005, Currenti 2010, Elsabbagh et al. 2012, Ferreri 2014.

References

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Edit history

Date	Action	Author
2017-05-11	Created	Orlic-Milacic M
2017-10-03	Authored	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

Date	Action	Author
2018-08-09	Modified	Orlic-Milacic M

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
MECP2	P51608-1, P51608-2	NCOR1	O75376	PRKACA	P17612

21. Disorders of Nervous System Development ([R-HSA-9697154](#))



Diseases: nervous system disease.

Neurodevelopmental disorders are chronic disorders that affect the function of the central nervous system (CNS) and impair motor skills, cognition, communication and/or behavior. While these disorders frequently stem from mutations in genes that directly control CNS development, they can also be a consequence of environmental insults such as hypoxic/ischemic injury, trauma, exposure to toxins, infections and nutritional deficiencies, or be indirectly caused by mutations in metabolic genes (reviewed by Ismail and Shapiro 2019). Disorders of nervous system development have been traditionally classified based on phenotypic traits (clinical presentation). Molecular genetics studies have revealed, however, that indistinguishable clinical presentations may result from pathogenic variants in different genes whose protein products function in connected biological pathways. On the other hand, distinct clinical presentations may be caused by pathogenic mutations in a single gene that functions in multiple biological pathways (Desikan and Bakrovich 2018). In the future, phenotype-based classification of neurodevelopmental disorders may be replaced by a more informative pathway-based nomenclature (Desikan and Bakrovich 2018). Biological pathways frequently impaired in neurodevelopmental disorders are signal transduction pathways such as the mTOR pathway in tuberous sclerosis complex (TSC) (Wong 2019) and the RAS/RAF/MAPK pathway in RASopathies (Kang and Lee 2019), neurotransmission pathways as in some autism spectrum disorders (ASD) (Burnashev and Szepetowski 2015, Hu et al. 2016), and pathways that regulate gene expression as in Mendelian disorders of epigenetic machinery (MDEM) (Fahrner and Bjornsson 2019).

So far, we have annotated the role of loss-of-function mutations in methyl-CpG-binding protein 2 (MECP2), an epigenetic regulator of transcription, in Rett syndrome, a pervasive developmental disorder that belongs to the MDEM category (Pickett and London 2005, Ferreri 2014).

References

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Wong M (2019). The role of glia in epilepsy, intellectual disability, and other neurodevelopmental disorders in tuberous sclerosis complex. *J Neurodev Disord*, 11, 30. [🔗](#)

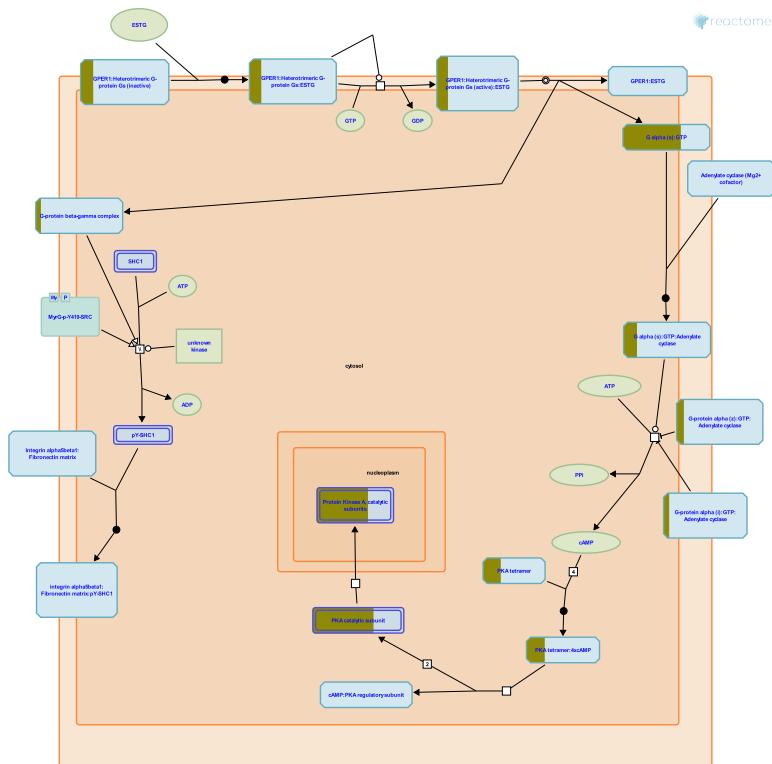
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Date	Action	Author
2020-08-06	Authored	Orlic-Milacic M
2020-08-06	Created	Orlic-Milacic M
2020-08-14	Reviewed	D'Eustachio P
2020-08-17	Edited	Orlic-Milacic M
2020-09-10	Modified	Orlic-Milacic M

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
MECP2	P51608-1, P51608-2	NCOR1	O75376	PRKACA	P17612

22. GPER1 signaling (R-HSA-9634597)



GPER1 (also known as GPR30) is an orphan G-protein coupled receptor that has been suggested to act as an alternate estrogen receptor (Revankar et al, 2005; Filardo et al, 2007; reviewed in Prossnitz and Barton, 2011; Gaudet et al, 2015). In support of this, a number of studies have shown that GPER1 stimulates MAPK and cAMP activation in response to estrogen in ESR1 negative breast cancer cells. Similar to classical ESR1-mediated signaling, this estrogen-responsive GPER1 is suggested to act through G beta gamma and to involve EGFR transactivation (Filardo et al, 2000; Filardo et al, 2002; reviewed in Filardo and Thomas, 2012).

References

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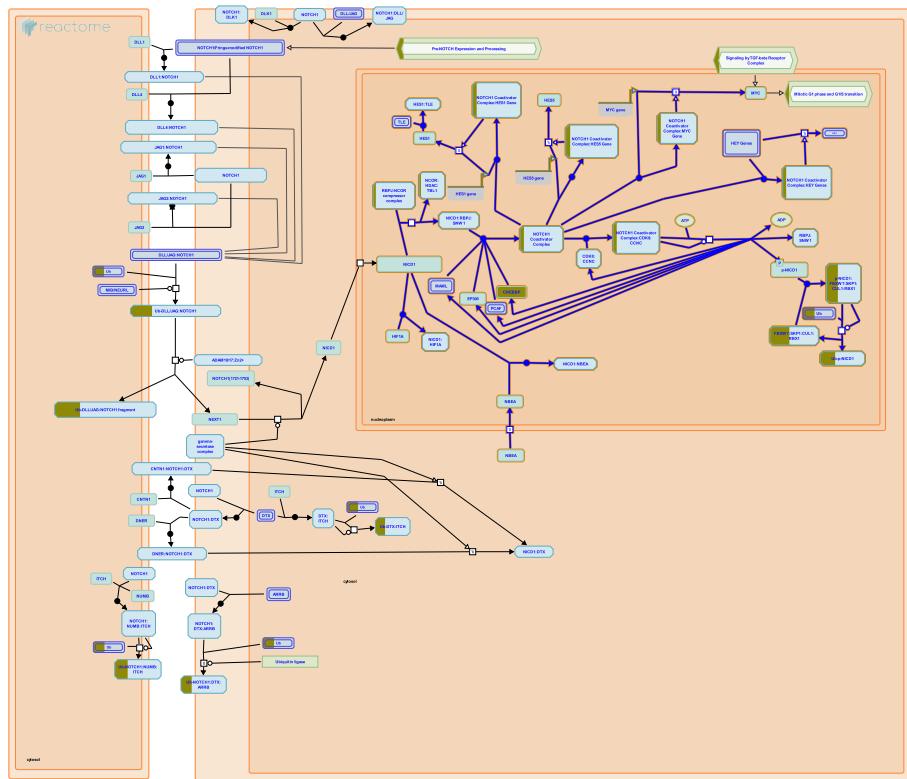
Edit history

Date	Action	Author
2018-12-15	Authored	Rothfels K
2019-01-11	Created	Rothfels K
2019-04-24	Reviewed	Acconcia F, Marino M
2021-11-09	Edited	Rothfels K
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
GNAI2	P04899	GNAS	P63092, Q5JWF2	GNAZ	P19086
GNB2	P62879	PRKACA	P17612, P22612		

23. NOTCH1 Intracellular Domain Regulates Transcription ([R-HSA-2122947](#))



Cellular compartments: nucleoplasm.

NICD1 produced by activation of NOTCH1 in response to Delta and Jagged ligands (DLL/JAG) presented in trans, traffics to the nucleus where it acts as a transcription regulator. In the nucleus, NICD1 displaces the NCOR corepressor complex from RBPJ (CSL). When bound to the co-repressor complex that includes NCOR proteins (NCOR1 and NCOR2) and HDAC histone deacetylases, RBPJ (CSL) represses transcription of NOTCH target genes (Kao et al. 1998, Zhou et al. 2000, Perissi et al. 2004, Perissi et al. 2008). Once the co-repressor complex is displaced, NICD1 recruits MAML (mastermind-like) to RBPJ, while MAML recruits histone acetyltransferases EP300 (p300) and PCAF, resulting in formation of the NOTCH coactivator complex that activates transcription from NOTCH regulatory elements. The minimal functional NOTCH coactivator complex that activates transcription from NOTCH regulatory elements is a heterotrimer composed of NICD, MAML and RBPJ (Fryer et al. 2002, Wallberg et al. 2002, Nam et al. 2006).

NOTCH1 coactivator complex is known to activate transcription of HES1 (Jarriault et al. 1995), HES5 (Arnett et al. 2010), HEY genes (Fischer et al. 2004, Leimeister et al. 2000, Maier et al. 2000, Arnett et al. 2010) and MYC (Palomero et al. 2006) and likely regulates transcription of many other genes (Wang et al. 2011). NOTCH1 coactivator complex on any specific regulatory element may involve additional transcriptional regulatory proteins. HES1 binds TLE proteins, forming an evolutionarily conserved transcriptional corepressor involved in regulation of neurogenesis, segmentation and sex determination (Grbavec et al. 1996, Fisher et al. 1996, Paroush et al. 1994).

After NOTCH1 coactivator complex is assembled on a NOTCH-responsive promoter, MAML (mastermind-like) recruits CDK8 in complex with cyclin C, triggering phosphorylation of conserved serine residues in TAD and PEST domains of NICD1 by CDK8. Phosphorylated NICD1 is recognized by the E3 ubiquitin ligase FBXW7 which ubiquitinates NICD1, leading to degradation of NICD1 and downregulation of NOTCH1 signaling. FBXW7-mediated ubiquitination and degradation of NOTCH1 depend on C-terminally located PEST domain sequences in NOTCH1 (Fryer et al. 2004, Oberg et al. 2001, Wu et al. 2001). The PEST domain of NOTCH1 and the substrate binding WD40 domain of FBXW7 are frequent targets of mutations in T-cell acute lymphoblastic leukemia - T-ALL (Welcker and Clurman 2008).

NICD1, which normally has a short half-life, can be stabilized by binding to the hypoxia-inducible factor 1-alpha (HIF1A) which accumulates in the nucleus when oxygen levels are low. This results in HIF1A-induced inhibition of cellular differentiation that is NOTCH-dependent (Gustafsson et al. 2005).

References

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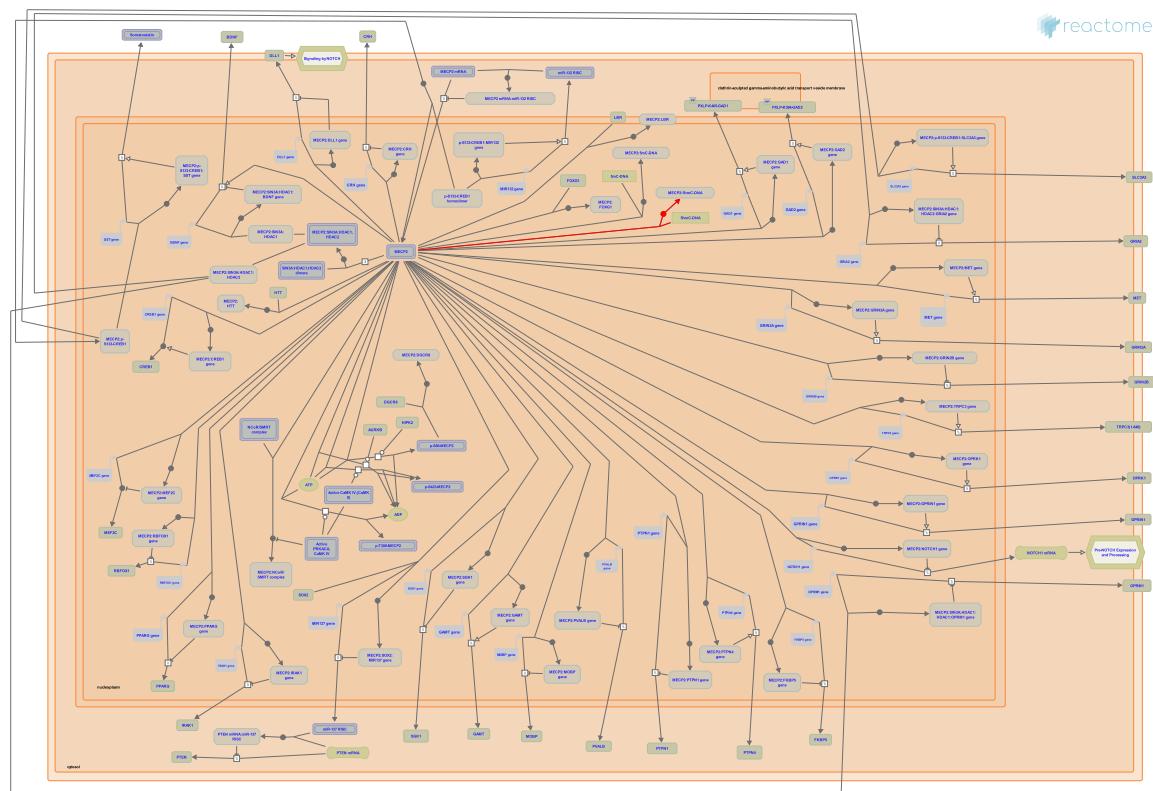
Edit history

Date	Action	Author
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
2012-02-14	Created	Orlic-Milacic M
2021-11-26	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
CREBBP	Q92793	FBXW7	Q969H0-1, Q969H0-4
NCOR1	O75376	UBB	P0CG47, P62979, P62987

24. Loss of MECP2 binding ability to 5hmC-DNA ([R-HSA-9022534](#))



Cellular compartments: nucleoplasm.

Diseases: Rett syndrome.

Missense mutations in the methyl-CpG binding domain (MBD) of MECP2, spanning amino acids 90 to 162, negatively affect the binding ability of MECP2 to hydroxymethylated DNA (Mellen et al. 2012).

References

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

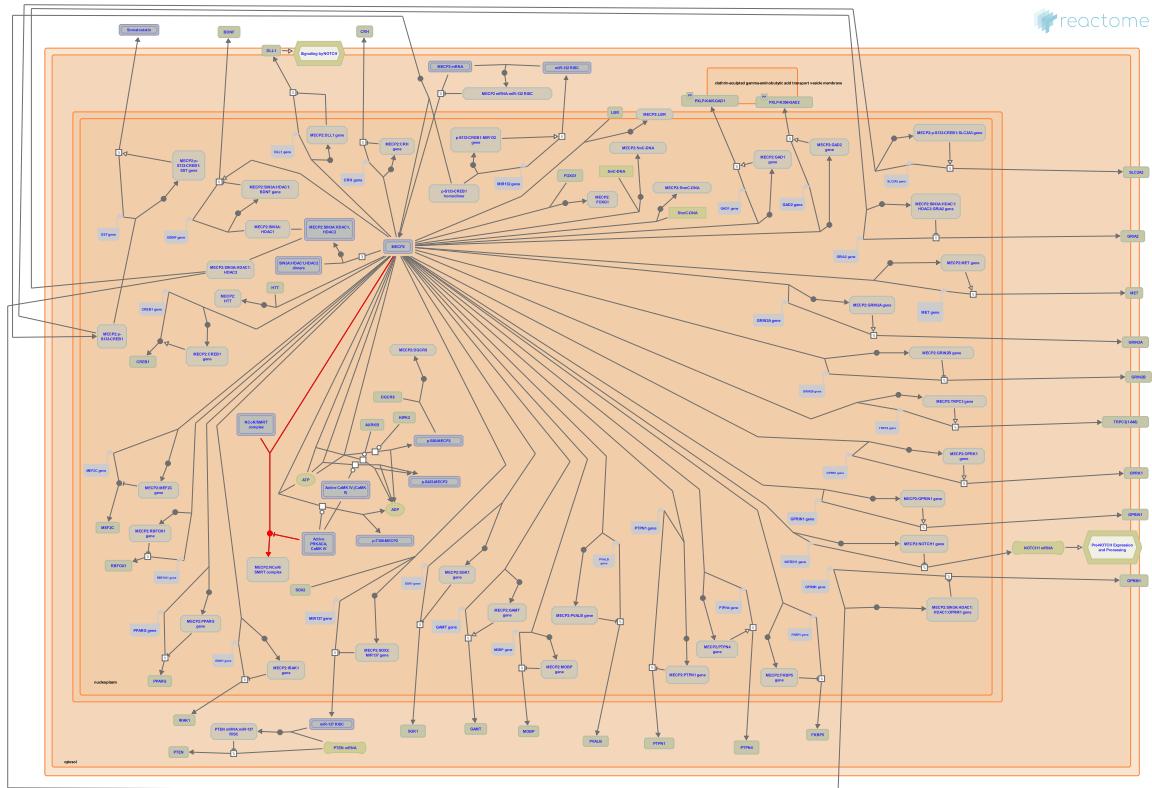
Edit history

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

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

25. Loss of MECP2 binding ability to the NCoR/SMRT complex (R-HSA-9022537)



Cellular compartments: nucleoplasm.

Diseases: Rett syndrome.

Missense mutations in the transcriptional repression domain of methyl-CpG-binding protein 2 (MECP2) can negatively affect binding of MECP2 to the nuclear receptor co-repressor (NCoR/SMRT) complex (Lyst et al. 2013, Ebert et al. 2013).

References

de Lima Alves F, Kastan NR, Guy J, Greenberg ME, Ekiert R, Bird A, ... Rappaport J (2013). Rett syndrome mutations abolish the interaction of MeCP2 with the NCoR/SMRT co-repressor. *Nat. Neurosci.*, 16, 898-902. [🔗](#)

Kastan NR, Greenberg ME, Ekiert R, Bird AP, Lyst MJ, Hu LS, ... Robinson ND (2013). Activity-dependent phosphorylation of MeCP2 threonine 308 regulates interaction with NCoR. *Nature*, 499, 341-5. [🔗](#)

Edit history

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

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

Input	UniProt Id	Input	UniProt Id
MECP2	P51608-1, P51608-2	NCOR1	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.

223 of the submitted entities were found, mapping to 282 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ABCA3	Q8WWZ4, Q99758	ABCC9	O60706	ABLIM1	O14639
ADAMTS2	O95450	AMPD2	Q01433	ANG	P03950
ANK2	Q01484	AP2A2	O94973-3	APOH	P02749
ARC	Q7LC44	ARHGEF17	Q96PE2	ARID1B	Q8NFD5
ARL13B	Q3SXY8	ATG14	Q6ZNE5	ATG4D	Q86TL0
ATN1	P54259	ATOX1	O00244	ATP13A1	Q9HD20
ATP2B1	P20020	ATP9B	O43861	BRP44	O95563
BSN	Q9UPA5	CACNA1H	O95180	CACNA2D2	Q9NY47
CACNB2	Q08289	CAMK2G	Q13555	CAPNS1	P04632, Q96L46
CBX6	O95503	CCND3	P30281	CD320	Q9NPF0
CDKN2A	P42771, P42772, Q8N726	CHCHD10	Q8WYQ3	CHD4	Q14839
CLU	P10909	CNIH2	Q6PI25	CREBBP	Q92793
CRH	P06850	CRMP1	Q14194	DCAF5	Q96JK2
DDR1	Q08345	DGCR8	Q8WYQ5	DLG5	Q8TDM6
DNAJC5	Q9H3Z4	DNM1	Q05193	DSCAM	O60469
EHMT1	Q9H9B1	EML4	Q9HC35	EP400	Q96L91
EPB41L3	Q9Y2J2	EPB49	Q08495	ETNK2	Q9NVF9
EVL	Q9UI08	FAM20C	Q8IXL6	FAP	P27487
FASN	P49327	FBXO41	Q8TF61	FBXW4	P57775
FBXW7	Q969H0-1, Q969H0-4	FOXO1	Q12778	FYN	P06241
GALNT14	Q96FL9	GC	P04062	GCFC2	P16383
GCG	P01275	GLI3	P10071	GLS	O94925
GNAI2	P04899	GNAS	P63092, Q5JWF2	GNAZ	P19086
GNB2	P62879	GNE	Q9Y223	GNMT	Q14749
GPC6	Q9Y625	GRHL1	Q9NZI5	GRIA3	P42263
HCFC1	P51610	HIST1H4E	P62805	HIVEP3	Q5T1R4
HMGCS1	Q01581	IGF2BP2	Q9Y6M1	IL10RA	P15260
IL6R	P08887, P08887-2	INHBA	P08476	INO80	Q9ULG1
IP6K2	Q9UHH9	ITPR1	Q14643	JAM3	Q9BX67
KANSL1	Q7Z3B3	KCNH2	Q12809	KCNK16	Q96T55
KDM4B	O94953	KIAA1009	Q5TB80	KLC2	Q6P597, Q9H0B6
KLHL5	Q96PQ7	LAMB1	P07942	LAMP1	P13473
LRRTM2	O43300	LSM7	Q9UK45	MAGED1	Q9Y5V3
MAU2	Q9Y6X3	MBOAT4	Q96T53	MDK	P21741
MECP2	P51608-1, P51608-2	MED19	A0JLT2	MINK1	Q8N4C8
MLL2	O14686, Q9UMN6	MLL4	O14686, Q9UMN6	MLLT4	P55196-2
MLXIPL	Q9NP71	MMP15	P51511	MPP2	Q08050
MRC1	P22897	MRPL33	O75394	MYBBP1A	Q9BQG0
MZT2B	Q6NZ67	NAB2	Q15742	NCOR1	O75376
NFIL3	Q16649	NGFRAP1	Q00994	NPC1L1	Q9UHC9-2
NPDC1	Q9NQX5	NPHP4	O75161	NR4A1	P22736

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ORAI2	Q96SN7	OSBP	P22059	OSBPL6	Q9BZF3
PAK4	O96013	PAPPA2	Q9BXP8	PARD6A	Q9NPB6
PARP14	Q460N5	PBX1	P40424	PCK1	P05771
PCNT	O95613	PCSK2	P16519	PDE9A	O76083
PDK4	Q16654	PFDN5	Q99471	PFKFB2	O60825
PHF2	O75151	PHF21A	Q96BD5	PHKA2	P46019
PI4KA	P42356	PITPNM2	O00562, Q9BZ72	PKD1	P98161
PLEKHA6	Q9Y2H5	PLEKHG6	Q3KR16	PLXNA1	Q9UIW2
PLXNA3	P51805	POFUT2	Q9Y2G5	POU2F1	P14859
PPFIA1	Q13136	PPY	P01298	PRKACA	P17612
PRKCE	Q02156	PTK2B	Q14289	PTPRN2	Q92932
PUM2	Q8TB72	RAMP2	O60895	RASGRP1	O95267
RBMX2	Q14088	REG3G	Q06141, Q6UW15	REG4	Q06141
RGL2	O15211	RGL3	Q3MIN7	RNF144A	P50876
RNF31	Q96EP0	RPS4Y1	P22090, Q8TD47	RRP36	Q96EU6
RYBP	Q8N488	SCARB1	Q8WTV0-2	SCMH1	Q96GD3-2
SEC16A	Q9NRR6	SERPINA10	Q9UK55	SETD1B	Q9UPS6
SETD9	Q8NE22	SH3KBP1	Q96B97	SLC22A17	Q8WUG5
SLC23A2	Q9UGH3	SLC25A27	O95847	SLC25A28	Q96A46
SLC2A3	P11169	SLC5A1	P13866, Q9NY91	SLC6A19	Q695T7
SLC6A4	P31645	SMPD1	P17405	SORBS1	Q9BX66
SOS2	Q07890	SPG7	Q9UQ90	SPOCK3	Q9BQ16
SPTB	P11277	SPTSSB	Q8NFR3	STAT4	Q14765
SULT4A1	Q9BR01	SYT7	O43581	TBC1D20	Q96BZ9
TCTN1	Q2MV58	TCTN2	Q96GX1	TESK1	Q15569
TRAF3IP1	Q8TDR0	TRAK1	Q9UPV9	TRAPPC2L	Q9UL33
TRAPPC9	Q96Q05	TRIM33	Q9UPN9	TRIM9	Q9C026
TRRAP	Q9Y4A5	TSPAN33	Q86UF1	TTR	P02766
TXNRD2	Q9NNW7	TYK2	P29597	UBB	P0CG47, P62979, P62987
UBOX5	O94941	USH1C	Q9Y6N9	USP24	Q9UPU5
VDR	P11473	WDR59	Q6PJI9	WDR60	Q8WVS4
WEE1	P30291, Q99640	WNT4	O96014, P56705	ZC3H6	Q8N5P1
ZFP36	P26651	ZNF264	O43296	ZNF331	Q9NQX6
ZNF91	Q9NQV7				

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
ARC	ENSG00000198576	CDKN2A	ENSG00000147889, ENST00000304494, ENST00000579755	CRH	ENSG00000147571
FASN	ENSG00000169710	FOXO1	ENSG00000150907	GCG	ENSG00000115263
GRHL1	ENSG00000134317	HMGCS1	ENSG00000112972	IL6R	ENSG00000160712
IP6K2	ENSG00000068745	KDM4B	ENSG00000127663	MECP2	ENST00000303391, ENST00000453960
MINK1	ENSG00000141503	NAB2	ENSG00000166886	PBX1	ENSG00000185630
PCK1	ENSG00000124253	POU2F1	ENSG00000143190	SLC2A3	ENSG00000059804
UBB	ENSG00000170315	WNT4	ENSG00000162552		

7. Identifiers not found

These 159 identifiers were not found neither mapped to any entity in Reactome.

ACAP3	ADNP	AFG3L1P	AHDC1	ALKBH1	ANGPTL1	APLP1	BAIAP3
BTBD11	BTBD2	BUD13	C11orf9	C15orf48	C17orf110	C19orf63	C19orf77
C20orf194	C21orf58	C4orf44	C5orf25	C5orf38	CAND2	CCDC153	CCDC72
CCDC93	CDHR3	CELSR3	CHD6	CHFR	CMIP	CPLX2	CPNE4
CRAMP1L	CRYBA2	DIP2C	DOPEY2	DUSP28	EIF4ENIF1	FAIM2	FAM110B
FAM160A2	FAM193A	FEV	FEZ1	FEZ2	FLJ43663	FLJ45340	GCFC1
GCNT2	GDAP1L1	GLIPR2	GOLGA7B	GON4L	GPR107	GPR3	GPR64
GPRASP1	GRINA	H6PD	HDGFRP3	HEG1	HMP19	HSD11B1L	IFI27L1
ILKAP	IRX2	KANSL1-AS1	KCTD5	KIAA0195	KIAA1244	KIAA1324	KLHDC4
LINC00271	LOC100130890	LOC100130899	LOC100505696	LOC100506930	LOC100507577	LOC146880	LOC389493
LOC401320	LRCH1	LRRC10B	LUST	MAP3K4	MAP3K9	MGC72080	MYEOV2
N4BP1	NEDD9	NENF	NKTR	ODF2L	PAPD5	PCDH17	PCDHB5
PCGF3	PCNXL3	PHF12	PLEKHH3	PPIG	PRICKLE2	PRPF4B	PRRC2B
PTPRT	PYROXD2	RASSF5	RAVER1	RBM33	RNASE4	RNASEK	RNF150
RPL32P3	RUFY3	SEC31B	SEPN1	SERF2	SERPINI2	SETD5	SEZ6L2
SGSM2	SHROOM2	SHROOM3	SIK3	SLIRP	SNED1	SNX29	SPPL3
SSBP3	SSH1	SSX2IP	STK35	STMN3	SUSD4	SYT13	TAOK2
TAPT1	TCTA	TM4SF4	TMEM161B	TMEM201	TMEM9	TMUB1	TPPP3
TRAPPC2P1	TSHZ1	TTC18	UBE2Q2P1	UBXN8	UNC119	VPS13A	WDFY3
WRNIP1	YTHDC2	ZMIZ1	ZNF526	ZNF814	ZNF821	ZXDC	