



# 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=MjAyMjAyMjYxODIwNDZfMTc0Mjc%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.

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# 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:

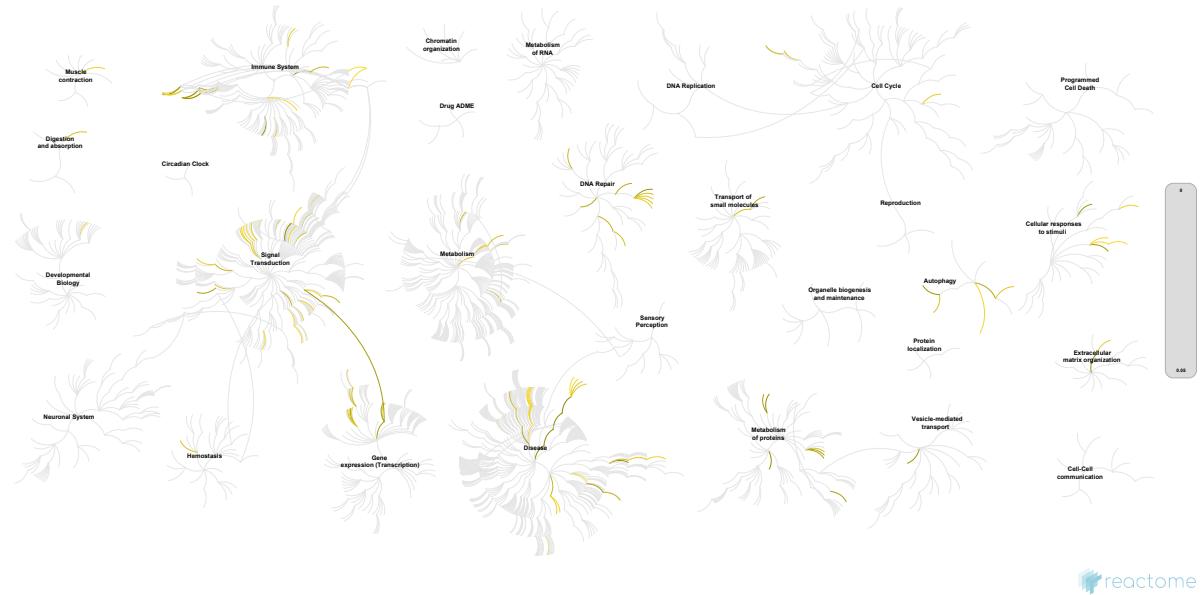
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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 Benjamini-Hochberg method. ↗
- 143 out of 279 identifiers in the sample were found in Reactome, where 837 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 MjAyMjAyMjYxODIwNDZfMTc0Mjc%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
NF-kB is activated and signals survival	4 / 15	9.95e-04	3.68e-04	0.037	3 / 4	2.93e-04
Signaling by NOTCH1 HD Domain Mutants in Cancer	4 / 16	0.001	4.68e-04	0.037	2 / 6	4.40e-04
Constitutive Signaling by NOTCH1 HD Domain Mutants	4 / 16	0.001	4.68e-04	0.037	2 / 6	4.40e-04
p75NTR recruits signalling complexes	4 / 16	0.001	4.68e-04	0.037	2 / 9	6.60e-04
FLT3 signaling by CBL mutants	3 / 7	4.64e-04	5.31e-04	0.037	1 / 1	7.33e-05
Attenuation phase	6 / 47	0.003	6.68e-04	0.037	3 / 5	3.66e-04
MAP3K8 (TPL2)-dependent MAPK1/3 activation	4 / 18	0.001	7.24e-04	0.037	4 / 8	5.86e-04
Maturation of protein E	3 / 8	5.31e-04	7.80e-04	0.037	1 / 5	3.66e-04
Maturation of protein E	3 / 8	5.31e-04	7.80e-04	0.037	1 / 5	3.66e-04
TICAM1, RIP1-mediated IKK complex recruitment	4 / 19	0.001	8.84e-04	0.038	2 / 3	2.20e-04
p75NTR signals via NF-kB	4 / 19	0.001	8.84e-04	0.038	5 / 13	9.53e-04
Loss of MECP2 binding ability to 5hmC-DNA	2 / 2	1.33e-04	9.29e-04	0.038	1 / 1	7.33e-05
Regulation of PTEN localization	3 / 10	6.64e-04	0.001	0.059	2 / 4	2.93e-04
NOTCH2 Activation and Transmission of Signal to the Nucleus	4 / 23	0.002	0.002	0.061	2 / 11	8.06e-04
Myoclonic epilepsy of Lafora	3 / 11	7.30e-04	0.002	0.061	1 / 2	1.47e-04
Downregulation of ERBB4 signaling	3 / 11	7.30e-04	0.002	0.061	2 / 5	3.66e-04
Modulation by Mtb of host immune system	3 / 11	7.30e-04	0.002	0.061	1 / 6	4.40e-04
PTK6 Regulates RTKs and Their Effectors AKT1 and DOK1	3 / 11	7.30e-04	0.002	0.061	1 / 8	5.86e-04
Glucagon signaling in metabolic regulation	5 / 40	0.003	0.002	0.061	5 / 6	4.40e-04
IKK complex recruitment mediated by RIP1	4 / 24	0.002	0.002	0.061	2 / 3	2.20e-04
HSF1-dependent transactivation	6 / 59	0.004	0.002	0.061	4 / 8	5.86e-04
IRAK2 mediated activation of TAK1 complex	3 / 12	7.96e-04	0.002	0.062	4 / 5	3.66e-04
HSF1 activation	5 / 43	0.003	0.003	0.067	1 / 7	5.13e-04

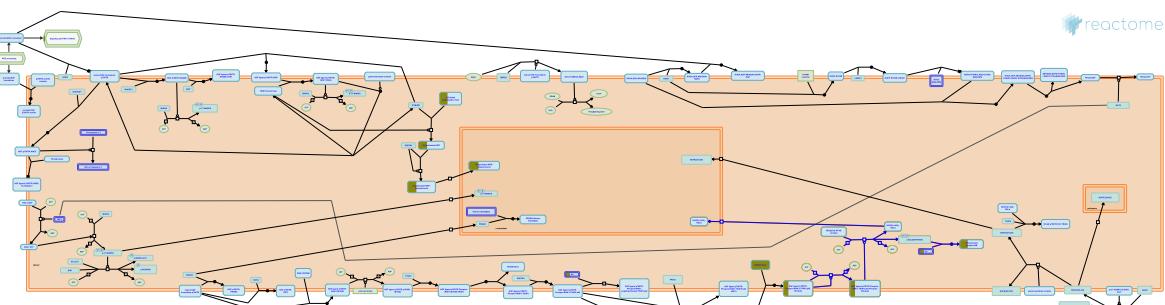
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Deactivation of the beta-catenin transactivating complex	5 / 44	0.003	0.003	0.071	2 / 14	0.001
TICAM1,TRAF6-dependent induction of TAK1 complex	3 / 13	8.63e-04	0.003	0.071	5 / 6	4.40e-04

\* 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. NF-kB is activated and signals survival (R-HSA-209560)



Upon activation in response to NGF, NF- $\kappa$ B moves to the nucleus, where it turns on genes that promote survival, and triggers the expression of HES1/5 to modulate dendritic growth.

### References

Mattson MP (2005). NF- $\kappa$ B in the survival and plasticity of neurons. *Neurochem Res*, 30, 883-93  
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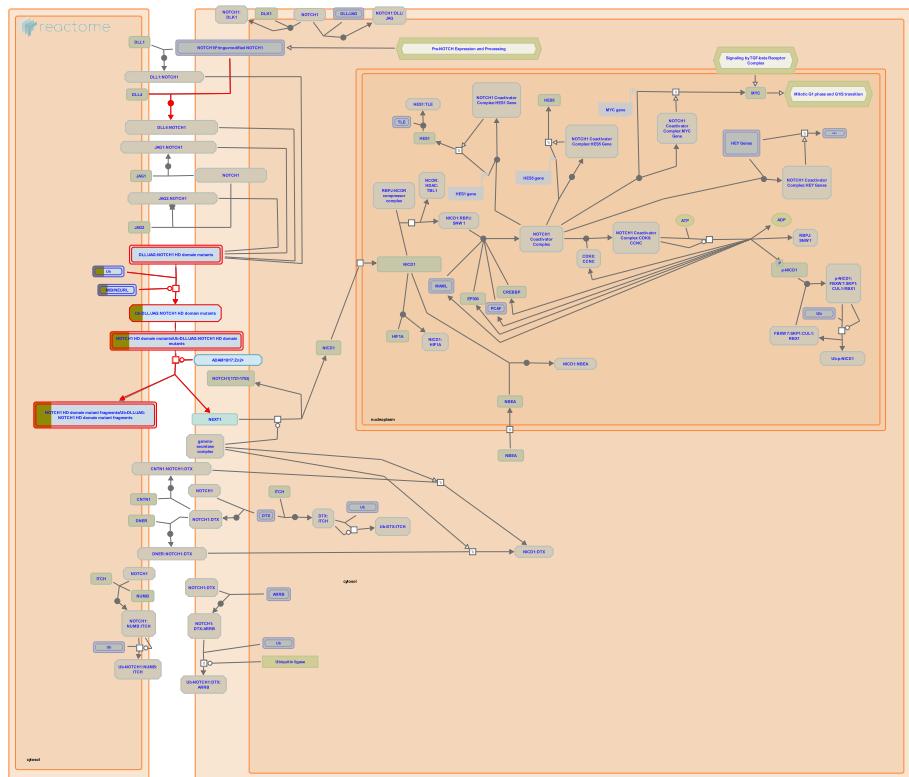
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Date	Action	Author
2006-10-10	Authored	Annibali D, Nasi S
2007-12-19	Created	Jassal B
2008-05-20	Edited	Jassal B
2008-05-20	Reviewed	Friedman WJ
2008-05-28	Reviewed	Chao MV
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
IKBKB	O14920	UBB	P0CG47, P62979, P62987

## 2. Signaling by NOTCH1 HD Domain Mutants in Cancer (R-HSA-2691230)



**Diseases:** cancer, T-cell leukemia.

NOTCH1 heterodimerization domain mutations are frequently found in T-cell acute lymphoblastic leukemia (T-ALL) (Weng et al. 2004) and result in constitutive activity of NOTCH1 mutants (Malecki et al. 2006).

### References

Lee W, Blacklow SC, Silverman LB, Look AT, Sanchez-Irizarry C, Aster JC, ... Morris JP 4th (2004). Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science*, 306, 269-71. [🔗](#)

Mitchell JL, Malecki MJ, Blacklow SC, Xu ML, Sanchez-Irizarry C, Aster JC & Histen G (2006). Leukemia-associated mutations within the NOTCH1 heterodimerization domain fall into at least two distinct mechanistic classes. *Mol. Cell. Biol.*, 26, 4642-51. [🔗](#)

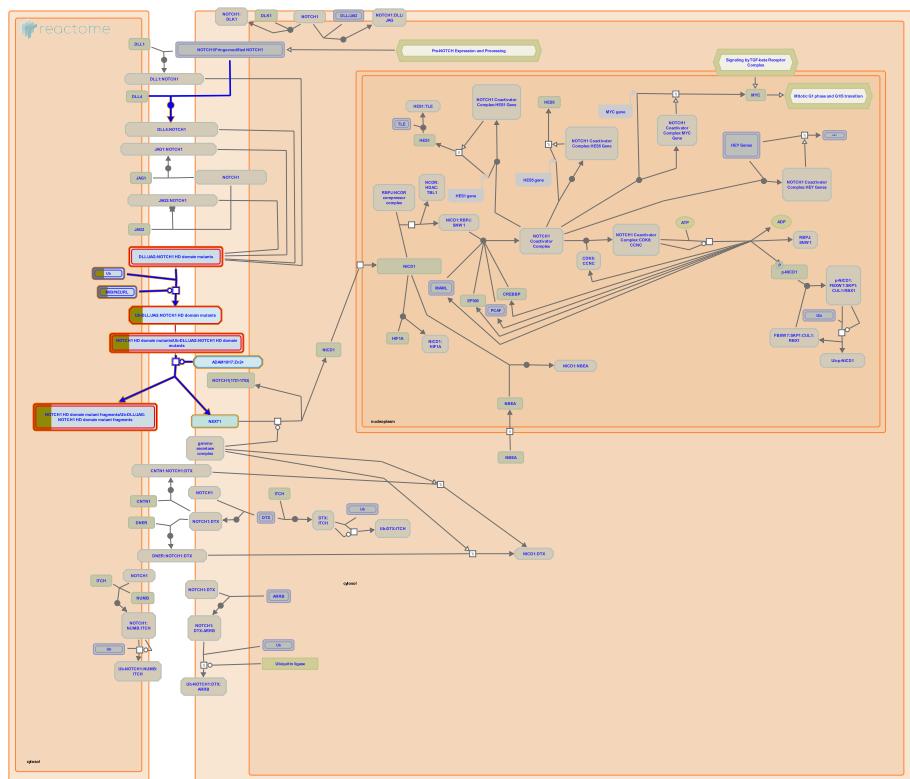
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2012-12-04	Created	Orlic-Milacic M
2013-01-04	Authored	Orlic-Milacic M
2013-01-09	Edited	Jassal B
2013-02-10	Reviewed	Haw R
2015-02-09	Modified	Wu G

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

Input	UniProt Id	Input	UniProt Id
NEURL1B	A8MQ27	UBB	P0CG47, P62979, P62987

### 3. Constitutive Signaling by NOTCH1 HD Domain Mutants (R-HSA-2691232)



**Diseases:** cancer, T-cell leukemia.

The heterodimerization (HD) domain of NOTCH1, responsible for association of NOTCH1 extracellular and transmembrane regions after furin-mediated cleavage of NOTCH1 precursor, is one of the hotspots for gain-of-function NOTCH1 mutations in T-cell acute lymphoblastic leukemia (T-ALL) (Weng et al. 2004). NOTCH1 HD domain mutants are responsive to ligand binding, but the activation (through cleavage of S2 and S3 sites and release of the intracellular domain NICD1) also happens spontaneously, in the absence of DLL and JAG ligands (Malecki et al. 2006). The following NOTCH1 HD domain mutants were directly functionally studied by Malecki et al.: NOTCH1 V1576E, NOTCH1 F1592S, NOTCH1 L1593P, NOTCH1 L1596H, NOTCH1 R1598P, NOTCH1 I1616N, NOTCH1 I1616T, NOTCH1 V1676D, NOTCH1 L1678P, NOTCH1 I1680N, NOTCH1 A1701P and NOTCH1 I1718T; other frequent NOTCH1 HD domain mutants (NOTCH1 L1574P, NOTCH1 L1574Q and NOTCH1 L1600P) are assumed to behave in a similar way.

### References

- Lee W, Blacklow SC, Silverman LB, Look AT, Sanchez-Irizarry C, Aster JC, ... Morris JP 4th (2004). Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. *Science*, 306, 269-71. [\[link\]](#)
- Mitchell JL, Malecki MJ, Blacklow SC, Xu ML, Sanchez-Irizarry C, Aster JC & Histen G (2006). Leukemia-associated mutations within the NOTCH1 heterodimerization domain fall into at least two distinct mechanistic classes. *Mol. Cell. Biol.*, 26, 4642-51. [\[link\]](#)

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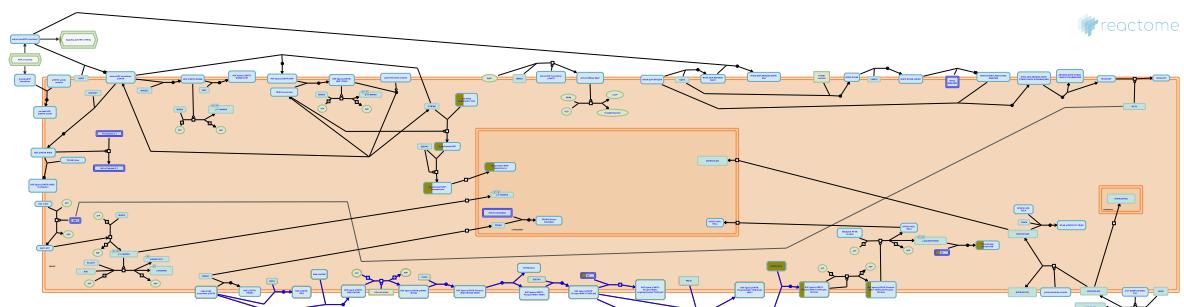
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Date	Action	Author
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2013-01-09	Edited	Jassal B
2013-02-10	Reviewed	Haw R
2013-02-11	Modified	Orlic-Milacic M

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

Input	UniProt Id	Input	UniProt Id
NEURL1B	A8MQ27	UBB	P0CG47, P62979, P62987

#### 4. p75NTR recruits signalling complexes (R-HSA-209543)



NF- $\kappa$ B activation involves recruitment at the cell membrane of several proteins such as RIP2, MYD88, IRAK1, TRAF6, p62 and atypical PKC by the NGF:p75NTR complex.

#### References

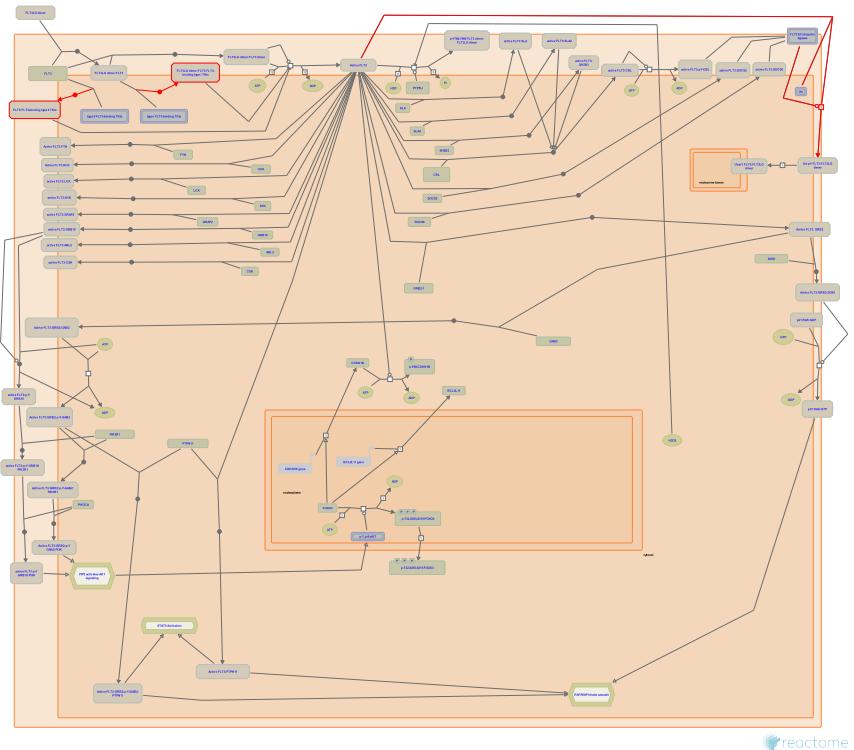
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2007-12-19	Created	Jassal B
2008-05-20	Edited	Jassal B
2008-05-20	Reviewed	Friedman WJ
2008-05-28	Reviewed	Chao MV
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
IKBKB	O14920	UBB	P0CG47, P62979, P62987

## 5. 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

- Rotmans G, Abbas S, Valk PJ & LÃ¶wenberg B (2008). Exon 8 splice site mutations in the gene encoding the E3-ligase CBL are associated with core binding factor acute myeloid leukemias. Haematologica, 93, 1595-7. [\[link\]](#)
- Buske C, Duyster J, Reindl C, Spiekermann K, Vempati S, Bohlander SK, ... Petropoulos K (2009). CBL exon 8/9 mutants activate the FLT3 pathway and cluster in core binding factor/11q deletion acute myeloid leukemia/myelodysplastic syndrome subtypes. Clin Cancer Res, 15, 2238-47. [\[link\]](#)
- Caligiuri MA, Perrotti D, Wei M, Arnoczky KJ, Wen J, Whitman SP, ... Briesewitz R (2007). Novel c-CBL and CBL-b ubiquitin ligase mutations in human acute myeloid leukemia. Blood, 110, 1022-4. [\[link\]](#)
- Berdel WE, Grundler R, Serve H, Duyster J, Brandts C, Tickenbrock L, ... Schmidt MHH (2007). Flt3-dependent transformation by inactivating c-Cbl mutations in AML. Blood, 110, 1004-12. [\[link\]](#)

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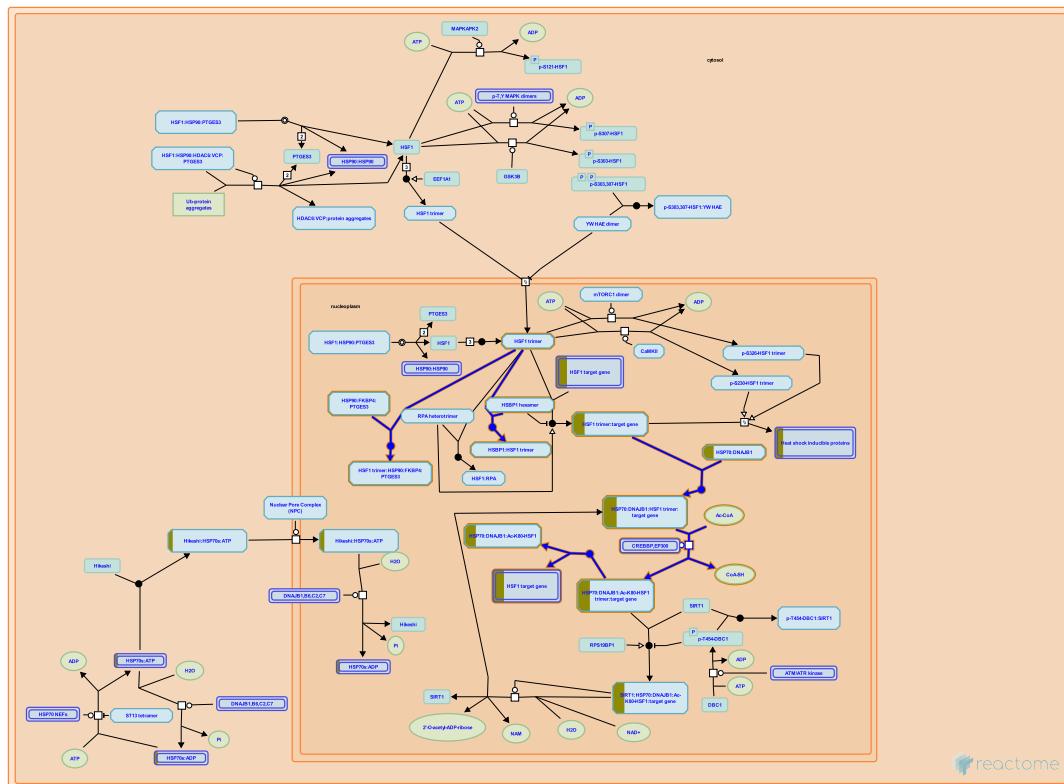
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2020-11-04	Created	Rothfels K
2020-11-06	Modified	Rothfels K

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

## 6. Attenuation phase (R-HSA-3371568)



Attenuation of the heat shock transcriptional response occurs during continuous exposure to intermediate heat shock conditions or upon recovery from stress (Abravaya et al. 1991). The attenuation phase of HSF1 cycle involves the transcriptional silencing of HSF1 bound to HSE, the release of HSF1 trimers from HSE and dissociation of HSF1 trimers to monomers. HSF1-driven heat stress associated transcription was shown to depend on inducible and reversible acetylation of HSF1 at Lys80, which negatively regulates DNA binding activity of HSF1 (Westerheide SD et al. 2009). In addition, the attenuation of HSF1 activation takes place when enough HSP70/HSP40 is produced to saturate exposed hydrophobic regions of proteins damaged as a result of heat exposure. The excess HSP70/HSP40 binds to HSF1 trimer, which leads to its dissociation from the promoter and conversion to the inactive monomeric form (Abravaya et al. 1991; Shi Y et al. 1998). Interaction of HSP70 with the transcriptional corepressor repressor element 1-silencing transcription factor corepressor (CoREST) assists in terminating heat-shock response (Gomez AV et al. 2008). HSF1 DNA-binding and transactivation activity were also inhibited upon interaction of HSF1-binding protein (HSBP1) with active trimeric HSF1(Satyal SH et al. 1998).

## References

Morimoto RI, Abravaya K & Phillips B (1991). Attenuation of the heat shock response in HeLa cells is mediated by the release of bound heat shock transcription factor and is modulated by changes in growth and in heat shock temperatures. *Genes Dev.*, 5, 2117-27.

## Edit history

Date	Action	Author
2013-05-13	Created	Shamovsky V
2013-10-29	Authored	Shamovsky V

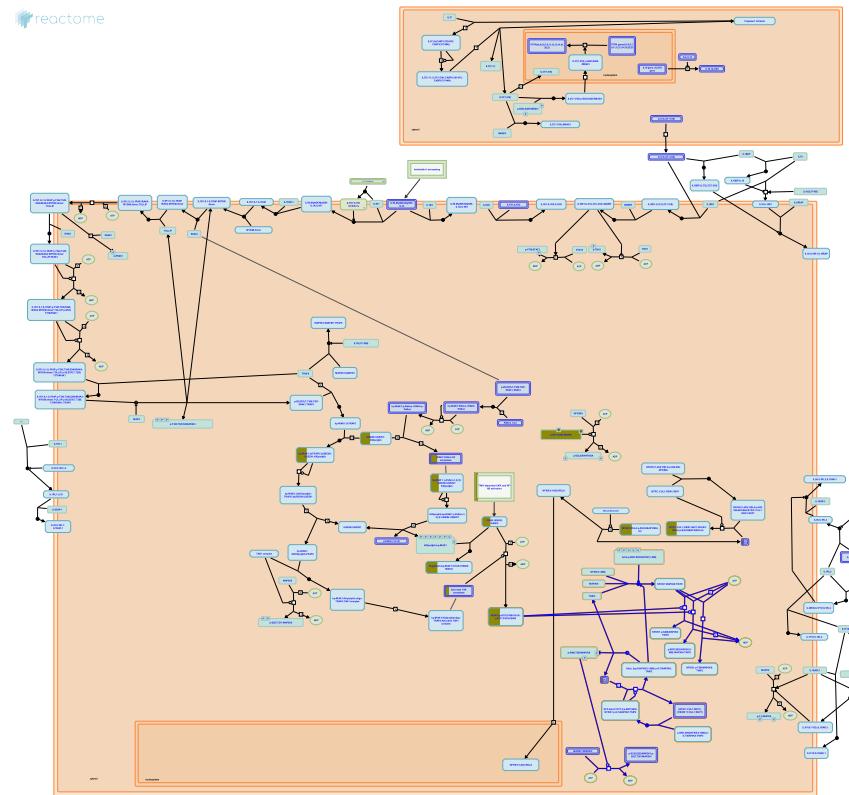
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2014-02-17	Edited	Shamovsky V
2014-02-17	Reviewed	Pani B
2021-11-28	Modified	Weiser JD

## 2 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id
HSPA1L	P34931

Input	Ensembl Id	Input	Ensembl Id
HSPA1L	ENSG00000206383, ENSG00000226704, ENSG00000234258, ENSG00000236251	UBB	ENSG00000170315

## 7. MAP3K8 (TPL2)-dependent MAPK1/3 activation (R-HSA-5684264)



Tumor progression locus-2 (TPL2, also known as COT and MAP3K8) functions as a mitogen-activated protein kinase (MAPK) kinase kinase (MAP3K) in various stress-responsive signaling cascades. MAP3K8 (TPL2) mediates phosphorylation of MAP2Ks (MEK1/2) which in turn phosphorylate MAPK (ERK1/2) (Gantke T et al., 2011).

In the absence of extra-cellular signals, cytosolic MAP3K8 (TPL2) is held inactive in the complex with ABIN2 (TNIP2) and NF $\kappa$ B p105 (NFKB1) (Beinke S et al., 2003; Waterfield MR et al., 2003; Lang V et al., 2004). This interaction stabilizes MAP3K8 (TPL2) but also prevents MAP3K8 and NF $\kappa$ B from activating their downstream signaling cascades by inhibiting the kinase activity of MAP3K8 and the proteolysis of NF $\kappa$ B precursor protein p105. Upon activation of MAP3K8 by various stimuli (such as LPS, TNF-alpha, and IL-1 beta), IKBKB phosphorylates NF $\kappa$ B p105 (NFKB1) at Ser927 and Ser932, which trigger p105 proteasomal degradation and releases MAP3K8 from the complex (Beinke S et al., 2003, 2004; Roget K et al., 2012). Simultaneously, MAP3K8 is activated by auto- and/or trans-phosphorylation (Gantke T et al. 2011; Yang HT et al. 2012). The released active MAP3K8 phosphorylates its substrates, MAP2Ks. The free MAP3K8, however, is also unstable and is targeted for proteasome-mediated degradation, thus restricting prolonged activation of MAP3K8 (TPL2) and its downstream signaling pathways (Waterfield MR et al. 2003; Cho J et al., 2005). Furthermore, partially degraded NF $\kappa$ B p105 (NFKB1) into p50 can dimerize with other NF $\kappa$ B family members to regulate the transcription of target genes.

MAP3K8 activity is thought to regulate the dynamics of transcription factors that control an expression of diverse genes involved in growth, differentiation, and inflammation. Suppressing the MAP3K8 kinase activity with selective inhibitors, such as C8-chloronaphthyridine-3-carbonitrile, caused a significant reduction in TNF $\alpha$  production in LPS- and IL-1 $\beta$ -induced both primary human monocytes and human blood (Hall JP et al. 2007). Similar results have been reported for mouse LPS-stimulated RAW264.7 cells (Hirata K et al. 2010). Moreover, LPS-stimulated macrophages derived from Map3k8 knockout mice secreted lower levels of pro-inflammatory cytokines such as TNF $\alpha$ , Cox2, Pge2 and CXCL1 (Dumitru CD et al. 2000; Eliopoulos AG et al. 2002). Additionally, bone marrow-derived dendritic cells (BMDCs) and macrophages from Map3k8 knockout mice showed significantly lower expression of IL-1 $\beta$  in response to LPS, poly IC and LPS/MDP (Mielke et al., 2009). However, several other studies seem to contradict these findings and Map3k8 deficiency in mice has been also reported to enhance pro-inflammatory profiles. Map3k8 deficiency in LPS-stimulated macrophages was associated with an increase in nitric oxide synthase 2 (NOS2) expression (LÃ³pez-PelÃ¡ez et al., 2011). Similarly, expression of IRAK-M, whose function is to compete with IL-1R-associated kinase (IRAK) family of kinases, was decreased in Map3k8-/ macrophages while levels of TNF and IL6 were elevated (Zacharioudaki et al., 2009). Moreover, significantly higher inflammation level was observed in 12-O-tetradecanoylphorbol-13-acetate (TPA)-treated Map3k8-/ mouse skin compared to WT skin (DeCicco-Skinner K. et al., 2011). Additionally, MAP3K8 activity is associated with NF $\kappa$ B inflammatory pathway. High levels of active p65 NF $\kappa$ B were observed in the nucleus of Map3k8 -/ mouse keratinocytes that dramatically increased within 15-30 minutes of TPA treatment. Similarly, increased p65 NF $\kappa$ B was observed in Map3k8-deficient BMDC both basally and after stimulation with LPS when compared to wild type controls (Mielke et al., 2009). The data opposes the findings that Map3k8-deficient mouse embryo fibroblasts and human Jurkat T cells with kinase domain-deficient protein have a reduction in NF $\kappa$ B activation but only when certain stimuli are administered (Lin et al., 1999; Das S et al., 2005). Thus, it is possible that whether MAP3K8 serves more of a pro-inflammatory or anti-inflammatory role may depend on cell- or tissue type and on stimuli (LPS vs. TPA, etc.) (Mielke et al., 2009; DeCicco-Skinner K. et al., 2012).

MAP3K8 has been also studied in the context of carcinogenesis, however the physiological role of MAP3K8 in the etiology of human cancers is also convoluted (Vougioukalaki M et al., 2011; DeCicco-Skinner K. et al., 2012).

## References

- Ley SC, Brender C, Handley M, Belich M, Janzen J, Papoutsopoulou S, ... Yang HT (2012). Coordinate regulation of TPL-2 and NF- $\kappa$ B signaling in macrophages by NF- $\kappa$ B1 p105. Mol. Cell. Biol., 32, 3438-51. [\[2\]](#)
- Ley SC, Sriskantharajah S & Gantke T (2011). Regulation and function of TPL-2, an I $\kappa$ B kinase-regulated MAP kinase kinase kinase. Cell Res., 21, 131-45. [\[3\]](#)
- Da Silva Xavier G (2012). *The Role of Tpl2 Protein Kinase in Carcinogenesis and Inflammation, Advances in Protein Kinases*.

## Edit history

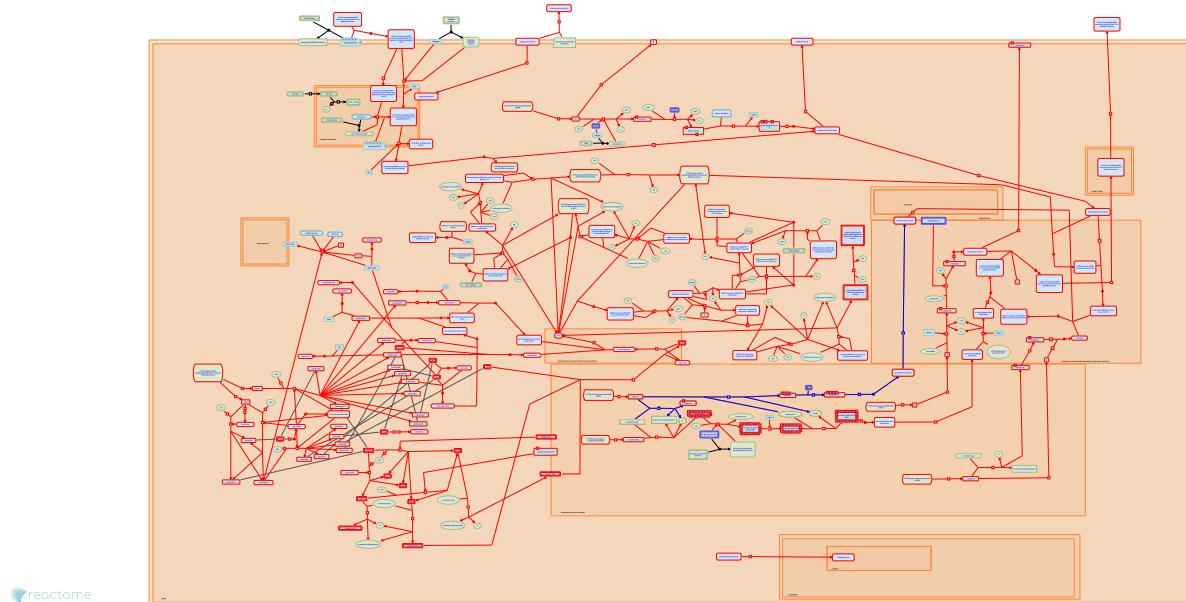
Date	Action	Author
2015-03-20	Created	Shamovsky V
2015-04-14	Reviewed	Jupe S

Date	Action	Author
2015-05-13	Authored	Shamovsky V
2015-08-21	Reviewed	DeCicco-Skinner KL
2015-08-25	Edited	Shamovsky V
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
IKBKB	O14920	UBB	P0CG47, P62979, P62987

## 8. Maturation of protein E (R-HSA-9683683)



**Diseases:** severe acute respiratory syndrome.

The envelope protein (E) gets palmitoylated and ubiquitinated after translation. It forms trimers that show porin activity but does not localize to the cell membrane (Tan et al, 2004; Liao et al, 2006; Alvarez et al, 2011).

### References

- Liu DX, Liao Y, Tam JP & Lescar J (2004). Expression of SARS-coronavirus envelope protein in *Escherichia coli* cells alters membrane permeability. *Biochem. Biophys. Res. Commun.*, 325, 374-80. [🔗](#)
- Liu DX, Liao Y, Tam JP, Yuan Q & Torres J (2006). Biochemical and functional characterization of the membrane association and membrane permeabilizing activity of the severe acute respiratory syndrome coronavirus envelope protein. *Virology*, 349, 264-75. [🔗](#)
- Marcos-Villar L, Jiménez-Guardeño JM, DeDiego ML, Enjuanes L, Nieto-Torres JL & Alvarez E (2010). The envelope protein of severe acute respiratory syndrome coronavirus interacts with the non-structural protein 3 and is ubiquitinated. *Virology*, 402, 281-91. [🔗](#)

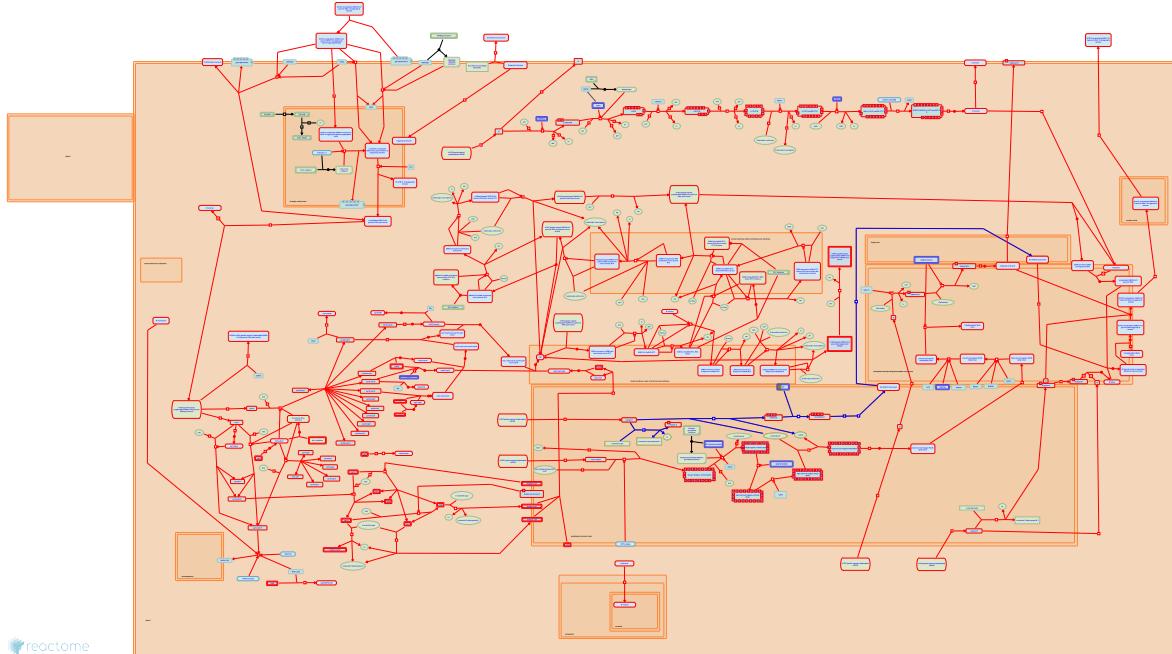
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Date	Action	Author
2020-04-08	Authored	Stephan R
2020-04-17	Created	Stephan R
2020-05-21	Edited	D'Eustachio P
2020-05-27	Reviewed	Mazein A, Acencio ML
2020-08-04	Modified	Gillespie ME

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 9. Maturation of protein E (R-HSA-9694493)



**Diseases:** COVID-19.

**Inferred from:** Maturation of protein E.

This COVID-19 pathway has been created by a combination of computational inference from SARS-CoV-1 data (<https://reactome.org/documentation/inferred-events>) and manual curation, as described in the summation for the overall SARS-CoV-2 infection pathway.

The envelope protein (E) gets palmitoylated and ubiquitinated after translation. It forms trimers that show porin activity but does not localize to the cell membrane (Tan et al, 2004; Liao et al, 2006; Alvarez et al, 2011)

### References

- Liu DX, Liao Y, Tam JP & Lescar J (2004). Expression of SARS-coronavirus envelope protein in Escherichia coli cells alters membrane permeability. *Biochem. Biophys. Res. Commun.*, 325, 374-80. [🔗](#)
- Liu DX, Liao Y, Tam JP, Yuan Q & Torres J (2006). Biochemical and functional characterization of the membrane association and membrane permeabilizing activity of the severe acute respiratory syndrome coronavirus envelope protein. *Virology*, 349, 264-75. [🔗](#)
- Marcos-Villar L, Jiménez-Guardeño JM, DeDiego ML, Enjuanes L, Nieto-Torres JL & Alvarez E (2010). The envelope protein of severe acute respiratory syndrome coronavirus interacts with the non-structural protein 3 and is ubiquitinated. *Virology*, 402, 281-91. [🔗](#)

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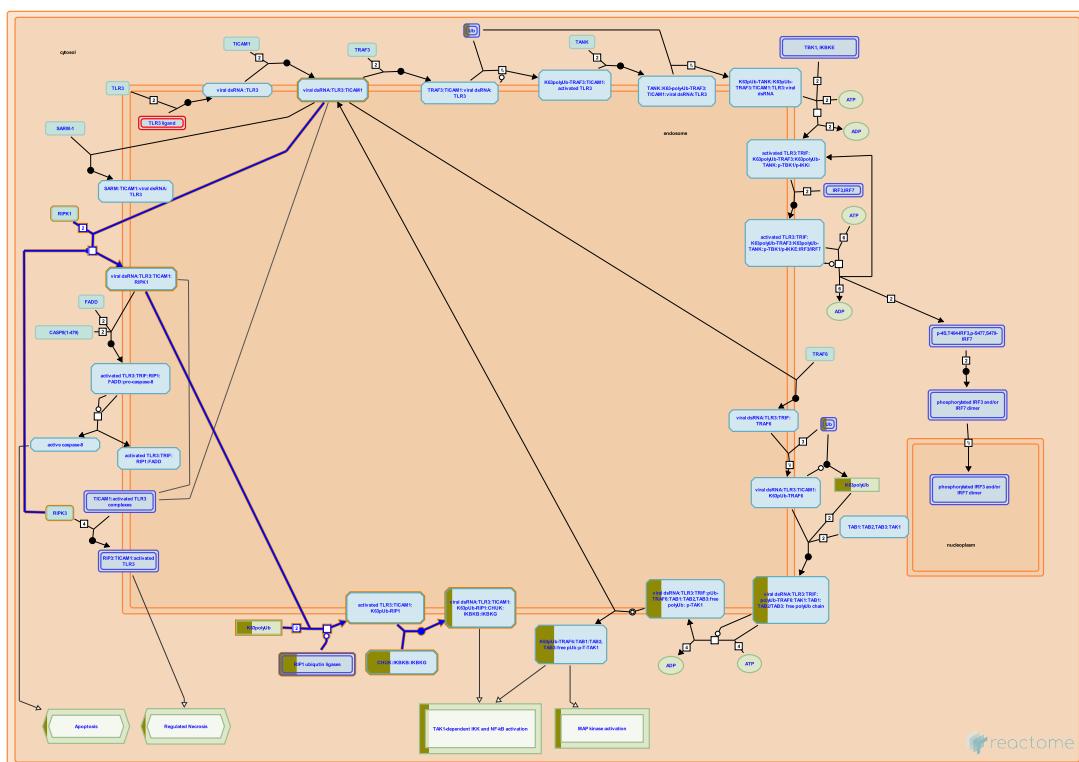
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2020-07-07	Created	Cook J
2020-08-28	Edited	Stephan R

Date	Action	Author
2020-08-28	Authored	Stephan R
2020-09-09	Modified	Gillespie ME
2020-09-09	Reviewed	Acencio ML

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 10. TICAM1, RIP1-mediated IKK complex recruitment (R-HSA-168927)



Receptor-interacting protein 1 (RIP1) mediates the activation of interferon-alpha/beta via intermediate activation of IKK/TBK1 or NF $\kappa$ B pathways.

### References

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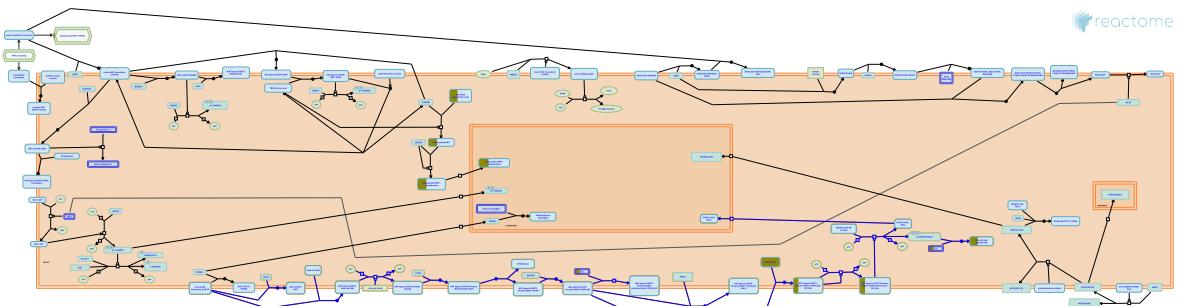
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Date	Action	Author
2005-11-10	Authored	Luo F
2005-11-22	Created	de Bono B
2006-04-24	Reviewed	Gay NJ
2009-09-29	Revised	Shamovsky V
2009-12-16	Edited	Shamovsky V
2012-11-13	Reviewed	Fitzgerald KA
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
IKBKB	O14920	UBB	P0CG47, P62979, P62987

## 11. p75NTR signals via NF-kB (R-HSA-193639)



The NF- $\kappa$ B pathway is an important pro-survival signalling pathway activated by mature NGF, but not BDNF or NT-3, through p75NTR. It is unclear whether TRKA activity also affects NF- $\kappa$ B activation.

## References

Memet S (2006). NF- $\kappa$ B functions in the nervous system: from development to disease. *Biochem Pharmacol*, 72, 1180-95. [View](#)

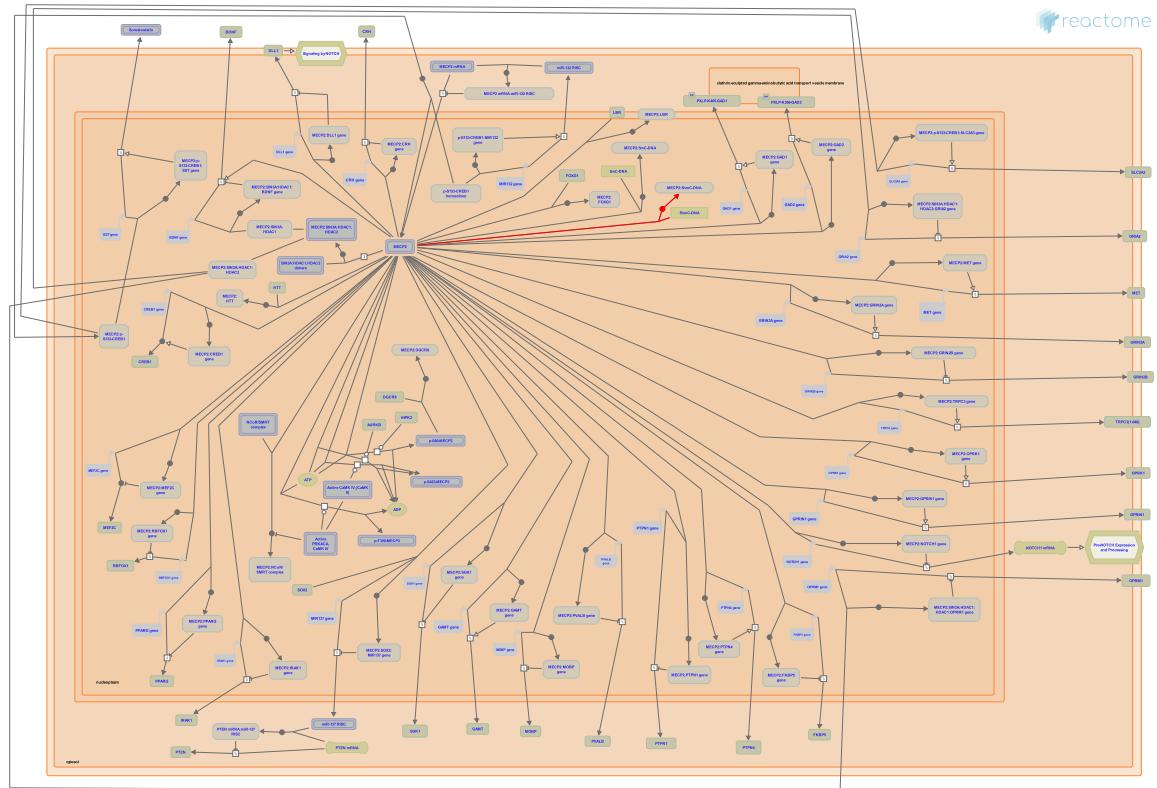
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Date	Action	Author
2006-10-10	Authored	Annibali D, Nasi S
2007-02-23	Created	Jassal B
2008-05-20	Edited	Jassal B
2008-05-20	Reviewed	Friedman WJ
2008-05-28	Reviewed	Chao MV
2021-11-26	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
IKBKB	O14920	UBB	P0CG47, P62979, P62987

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

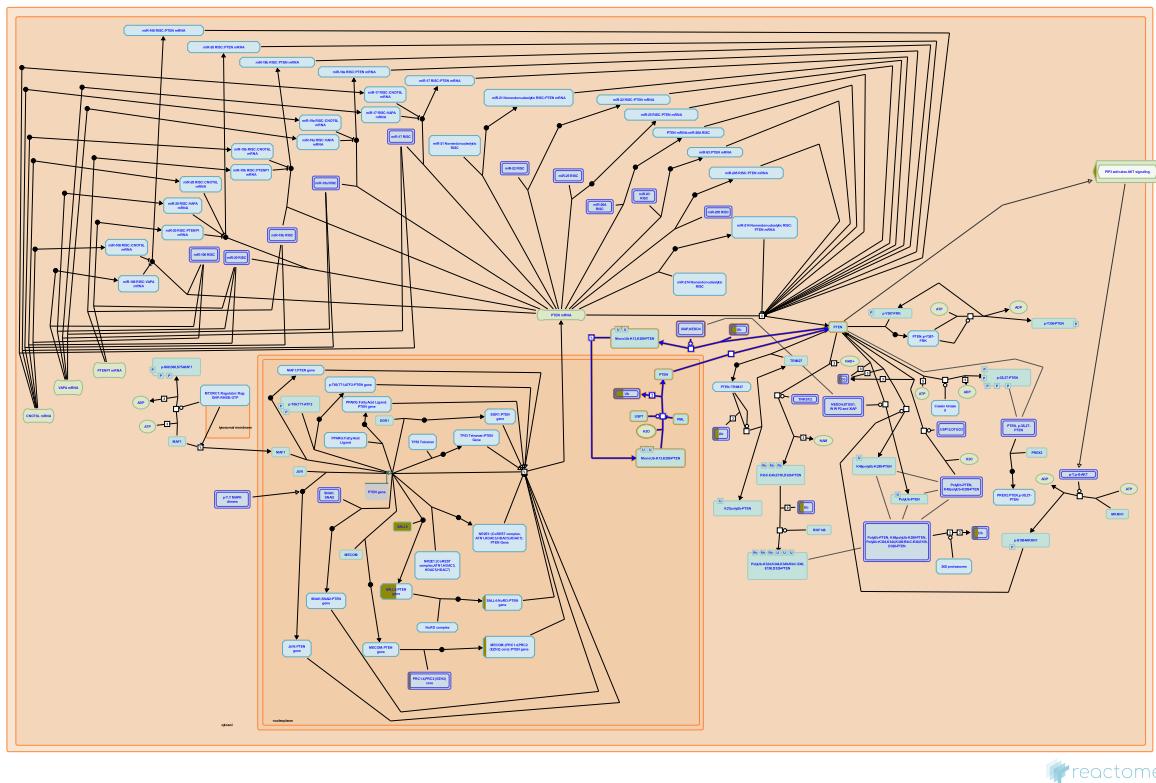
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2017-10-03	Authored	Orlic-Milacic M
2018-08-07	Reviewed	Christodoulou J, Krishnaraj R
2018-08-08	Modified	Orlic-Milacic M
2018-08-08	Edited	Orlic-Milacic M

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

Input	UniProt Id
MECP2	P51608-1, P51608-2

### 13. Regulation of PTEN localization (R-HSA-8948747)



When monoubiquitinated by E3 ubiquitin ligases XIAP and NEDD4, PTEN translocates from the cytosol to the nucleus (Trotman et al. 2007, Van Themsche et al. 2009). USP7 (HAUSP)-mediated deubiquitination of monoubiquitinated nuclear PTEN promotes relocalization of PTEN to the cytosol (Song et al. 2008).

## References

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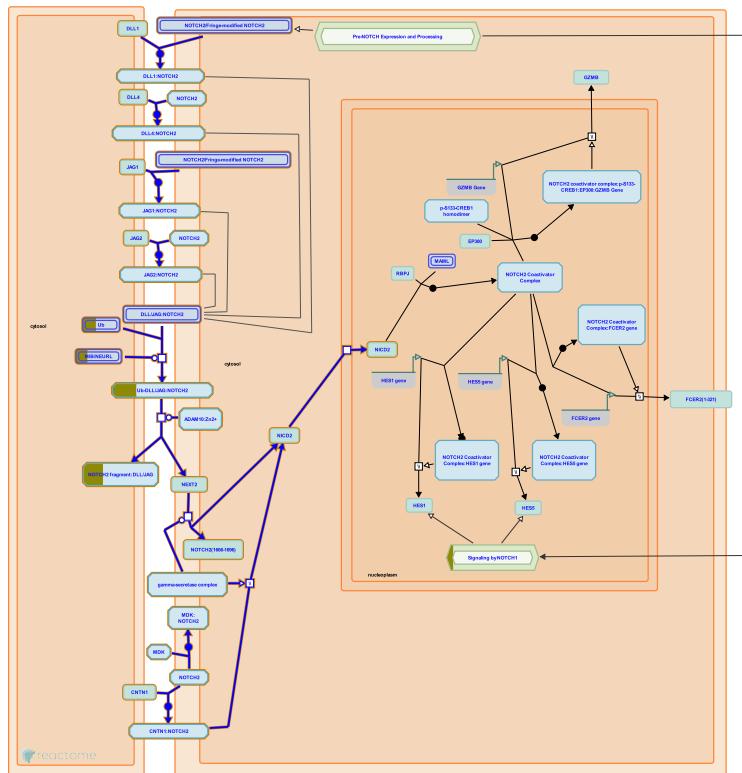
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2016-11-16	Authored	Orlic-Milacic M
2016-11-16	Created	Orlic-Milacic M
2017-05-09	Edited	Orlic-Milacic M
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 14. NOTCH2 Activation and Transmission of Signal to the Nucleus (R-HSA-2979096)



Similar to NOTCH1, NOTCH2 is activated by Delta-like and Jagged ligands (DLL/JAG) expressed in trans on a neighboring cell (Shimizu et al. 1999, Shimizu et al. 2000, Hicks et al. 2000, Ji et al. 2004). The activation triggers cleavage of NOTCH2, first by ADAM10 at the S2 cleavage site (Gibb et al. 2010, Shimizu et al. 2000), then by gamma-secretase at the S3 cleavage site (Saxena et al. 2001, De Strooper et al. 1999), resulting in the release of the intracellular domain of NOTCH2, NICD2, into the cytosol. NICD2 subsequently traffics to the nucleus where it acts as a transcription regulator.

While DLL and JAG ligands are well established, canonical NOTCH2 ligands, there is limited evidence that NOTCH2, similar to NOTCH1, can be activated by CNTN1 (contactin 1), a protein involved in oligodendrocyte maturation (Hu et al. 2003). MDK (midkine), which plays an important role in epithelial to mesenchymal transition, can also activate NOTCH2 signaling and is able to bind to the extracellular domain of NOTCH2, but the exact mechanism of MDK-induced NOTCH2 activation has not been elucidated (Huang et al. 2008, Gungor et al. 2011).

## References

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Huang Y, Wu F, Sidransky D, Ratovitski EA, Trink B & Hoque MO (2008). Midkine induces epithelial-mesenchymal transition through Notch2/Jak2-Stat3 signaling in human keratinocytes. *Cell Cycle*, 7, 1613-22. [🔗](#)

Izbicki JR, Gündüz C, Kalinina T, Vashist YK, Bockhorn M, Yekebas E, ... Zander H (2011). Notch signaling activated by replication stress-induced expression of midkine drives epithelial-mesenchymal transition and chemoresistance in pancreatic cancer. *Cancer Res.*, 71, 5009-19. [🔗](#)

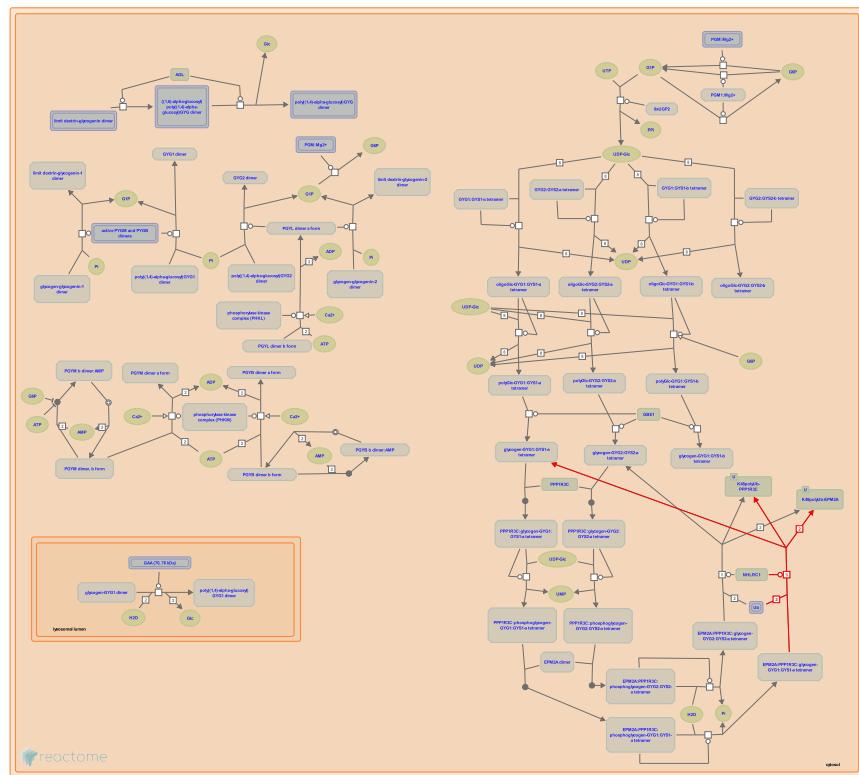
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2013-01-11	Authored	Orlic-Milacic M
2013-01-11	Created	Orlic-Milacic M
2013-01-14	Edited	Haw R
2013-04-25	Reviewed	Ilagan MXG, Boyle S
2021-11-26	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
NEURL1B	A8MQ27	UBB	P0CG47, P62979, P62987

## 15. Myoclonic epilepsy of Lafora (R-HSA-3785653)



**Diseases:** glycogen storage disease.

Lafora disease is a progressive neurodegenerative disorder with onset typically late in childhood, characterized by seizures and progressive neurological deterioration and death within ten years of onset. Recessive mutations in EPM2A (laforin) and NHLRC1 (malin) have been identified as causes of the disease. The disease is classified here as one of glycogen storage as EPM2A (laforin) and NHLRC1 (malin) regulate normal glycogen turnover and defects in either protein are associated with the formation of Lafora bodies, accumulations of abnormal, insoluble glycogen molecules in tissues including brain, muscle, liver, and heart (Ramachandran et al. 2009; Roach et al. 2012). Consistent with a central role for glycogen accumulation in the disease, reduced (Turnbull et al. 2011) or absent (Pederson et al. 2013) glycogen synthase activity prevents Lafora Disease in mouse models.

Type 2A disease. EPM2A (laforin) associated with cytosolic glycogen granules, normally catalyzes the removal of the phosphate groups added rarely but consistently to growing glycogen molecules (Tagliabracci et al. 2011). Defects in this catalytic activity lead to the formation of phosphorylated glycogen molecules that are insoluble and that show abnormal branching patterns (Minassian et al. 1998, Serratosa et al. 1999, Tagliabracci et al. 2011).

Type 2B disease. NHLRC1 (malin) normally mediates polyubiquitination of EPM2A (laforin) and PPP1R3C (PTG). The two polyubiquitinated proteins are targeted for proteasome-mediated degradation, leaving a glycogen-glycogenin particle associated with glycogen synthase. In the absence of NHLRC1 activity, EPM2A and PPP1R3C proteins appear to persist, associated with the formation of abnormal, stable glycogen granules (Lafora bodies) (Chan et al. 2003; Gentry et al. 2005). In NHLRC1 knockout mice PPP1R3C levels are unchanged rather than increased, suggesting that NHLRC1 does not target PPP1R3C for degradation. However, EPM2A protein levels are increased in this knockout consistent with NHLRC1's proposed role (DePaoli-Roach et al. 2010).

## References

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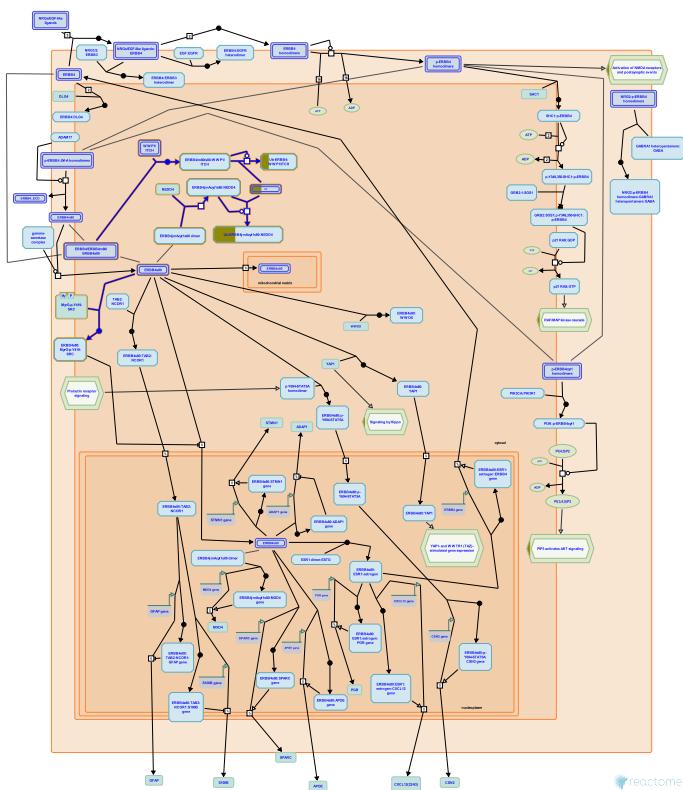
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2013-07-02	Created	D'Eustachio P
2013-07-19	Edited	D'Eustachio P
2013-07-19	Authored	D'Eustachio P
2014-02-19	Reviewed	Pederson B
2020-07-22	Modified	D'Eustachio P

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 16. Downregulation of ERBB4 signaling (R-HSA-1253288)



WW-domain binding motifs in the C-tail of ERBB4 play an important role in the downregulation of ERBB4 receptor signaling, enabling the interaction of intact ERBB4, ERBB4 m80 and ERBB4 s80 with NEDD4 family of E3 ubiquitin ligases WWP1 and ITCH. The interaction of WWP1 and ITCH with intact ERBB4 is independent of receptor activation and autophosphorylation. Binding of WWP1 and ITCH ubiquitin ligases leads to ubiquitination of ERBB4 and its cleavage products, and subsequent degradation through both proteasomal and lysosomal routes (Omerovic et al. 2007, Feng et al. 2009). In addition, the s80 cleavage product of ERBB4 JM-A CYT-1 isoform is the target of NEDD4 ubiquitin ligase. NEDD4 binds ERBB4 JM-A CYT-1 s80 (ERBB4jmAcyls80) through its PIK3R1 interaction site and mediates ERBB4jmAcyls80 ubiquitination, thereby decreasing the amount of ERBB4jmAcyls80 that reaches the nucleus (Zeng et al. 2009).

## References

### Edit history

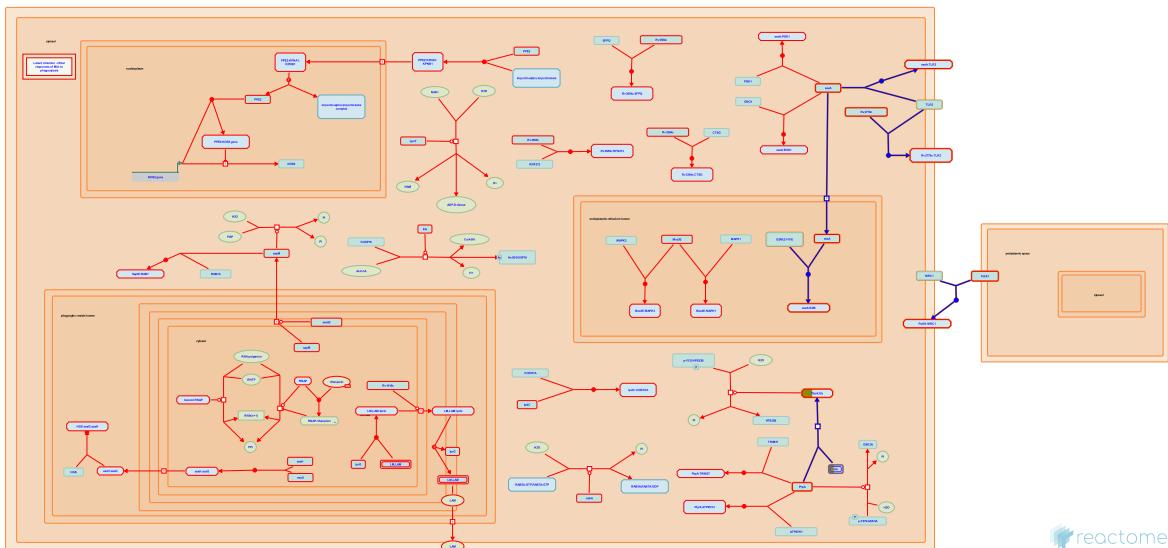
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2011-04-27	Created	Orlic-Milacic M
2011-11-04	Authored	Orlic-Milacic M
2011-11-07	Edited	Matthews L
2011-11-11	Reviewed	Zeng F, Harris RC
2012-02-20	Reviewed	Earp HS 3rd, Misior AM
2018-06-29	Revised	Orlic-Milacic M
2019-02-21	Revised	Stern DF
2019-02-21	Authored	Stern DF

Date	Action	Author
2019-03-06	Edited	Orlic-Milacic M
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

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



**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).

## References

Zenteno E, GarcÃa T, Esparza M, Mancilla R, Espinosa P & Palomares B (2015). PstS-1, the 38-kDa *Mycobacterium tuberculosis* glycoprotein, is an adhesin, which binds the macrophage mannose receptor and promotes phagocytosis. *Scand. J. Immunol.*, 81, 46-55. [View](#)

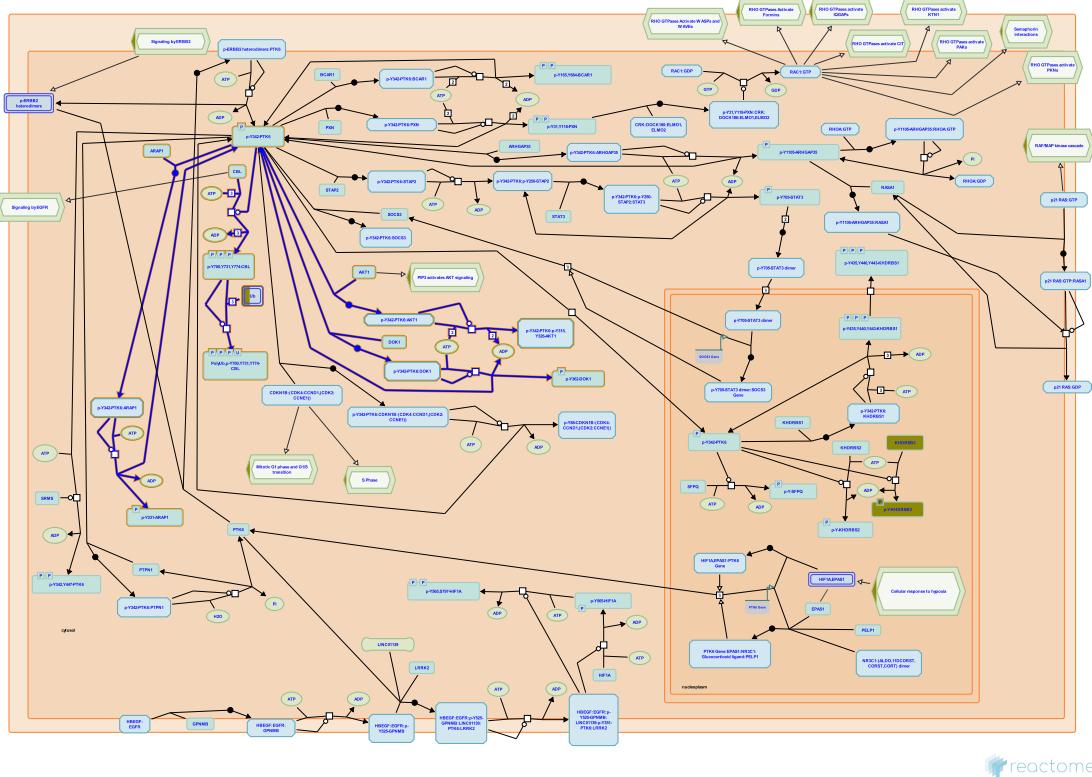
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Date	Action	Author
2019-02-19	Edited	Pardo AM
2019-02-19	Authored	Stephan R
2019-02-19	Created	Pardo AM
2019-10-23	Reviewed	Wilkinson RJ, Deffur A
2019-10-31	Modified	Matthews L

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 18. PTK6 Regulates RTKs and Their Effectors AKT1 and DOK1 (R-HSA-8849469)



PTK6 enhances EGFR signaling by inhibiting EGFR down-regulation (Kang et al. 2010, Li et al. 2012, Kang and Lee 2013). PTK6 may also enhance signaling by other receptor tyrosine kinases (RTKs), such as IGF1R (Fan et al. 2013) and ERBB3 (Kamalati et al. 2000).

PTK6 affects AKT1 activation (Zhang et al. 2005, Zheng et al. 2010) and targets negative regulator of RTKs, DOK1, for degradation (Miah et al. 2014).

### References

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- Lee ST & Kang SA (2013). PTK6 promotes degradation of c-Cbl through PTK6-mediated phosphorylation. *Biochem. Biophys. Res. Commun.*, 431, 734-9. [🔗](#)

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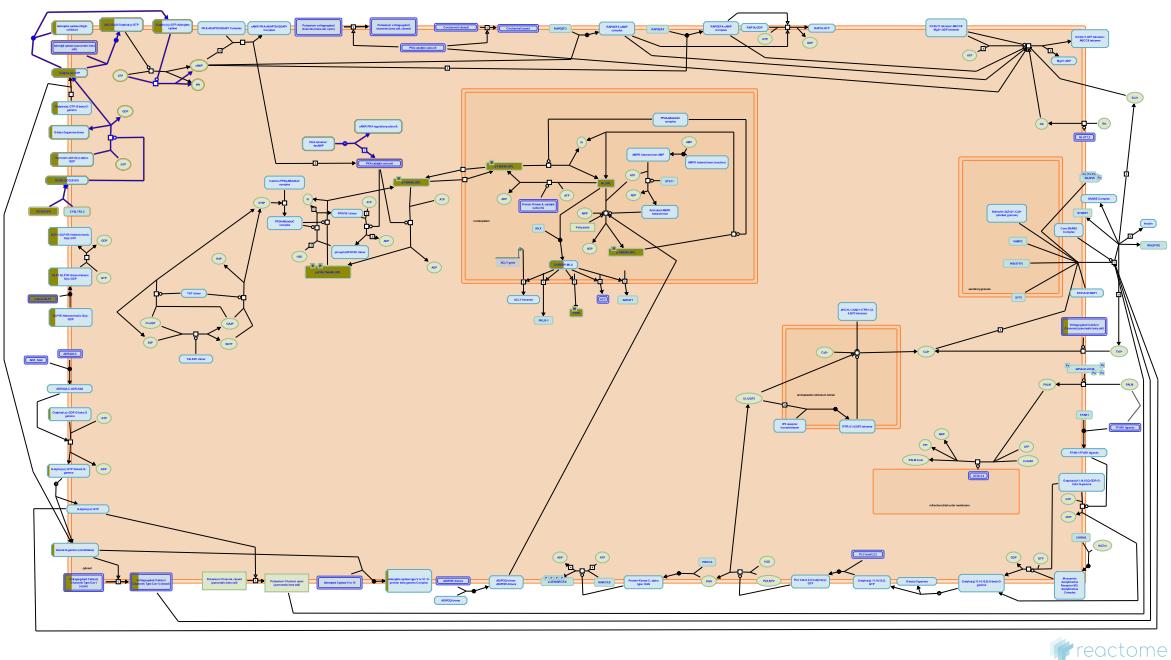
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Date	Action	Author
2016-01-05	Edited	Orlic-Milacic M
2016-01-05	Authored	Orlic-Milacic M
2016-02-07	Reviewed	Pires IM
2021-11-27	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

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



reactome

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

Zhang BB & Jiang G (2003). Glucagon and regulation of glucose metabolism. Am J Physiol Endocrinol Metab, 284, E671-8. [View](#)

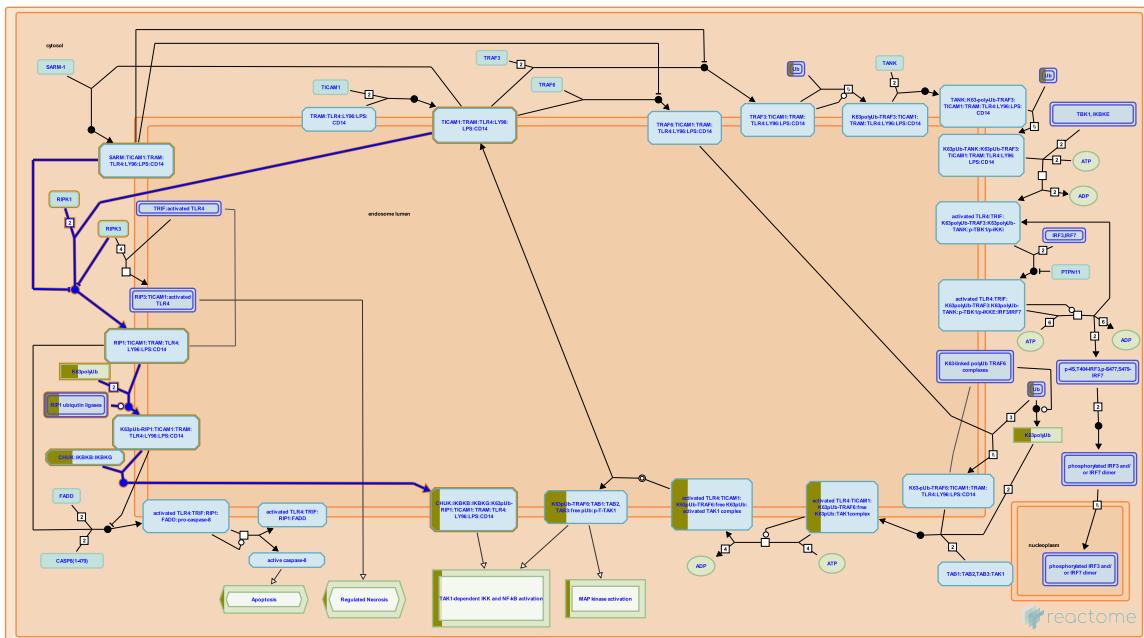
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Date	Action	Author
2005-04-28	Authored	Gopinathrao G
2005-04-28	Created	Gopinathrao G
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
ADCY4	Q8NFM4	GCG	P01275
GNAS	P63092, Q5JWF2	GNB2	P62879

## 20. IKK complex recruitment mediated by RIP1 (R-HSA-937041)



**Cellular compartments:** cytosol.

Receptor-interacting protein 1 (RIP1) mediates the activation of proinflammatory cytokines via intermediate induction of IKK complex in NF $\kappa$ B pathways [Ea et al. 2006]. Poly(I-C) treatment stimulated the recruitment of RIP1, TRAF6, and TAK1 to the TLR3 receptor complex in human embryonic kidney HEK293 transfected with FLAG-tagged TLR3 [Cusson-Hermance et al. 2005]. RIP1 was shown to be dispensable for TRIF-dependent activation of IRF3, which occurs in a TRIF/TBK1/IKK $\alpha$ -dependent manner [Cusson-Hermance et al. 2005, Sato et al. 2003]

## References

- Fitzgerald KA, Cusson-Hermance N, Khurana S, Kelliher MA & Lee TH (2005). Rip1 mediates the Trif-dependent toll-like receptor 3- and 4-induced NF- $\kappa$ B activation but does not contribute to interferon regulatory factor 3 activation. *J Biol Chem*, 280, 36560-6. [🔗](#)
- Deng L, Chen ZJ, Pineda G, Xia ZP & Ea CK (2006). Activation of IKK by TNFalpha requires site-specific ubiquitination of RIP1 and polyubiquitin binding by NEMO. *Mol Cell*, 22, 245-57. [🔗](#)
- Kawai T, Takeda K, Sato S, Akira S, Watanabe Y, Yamamoto M & Sugiyama M (2003). Toll/IL-1 receptor domain-containing adaptor inducing IFN-beta (TRIF) associates with TNF receptor-associated factor 6 and TANK-binding kinase 1, and activates two distinct transcription factors, NF- $\kappa$ B and IFN-regulatory factor-3, in the Toll-like receptor signaling. *J. Immunol.*, 171, 4304-10. [🔗](#)

## Edit history

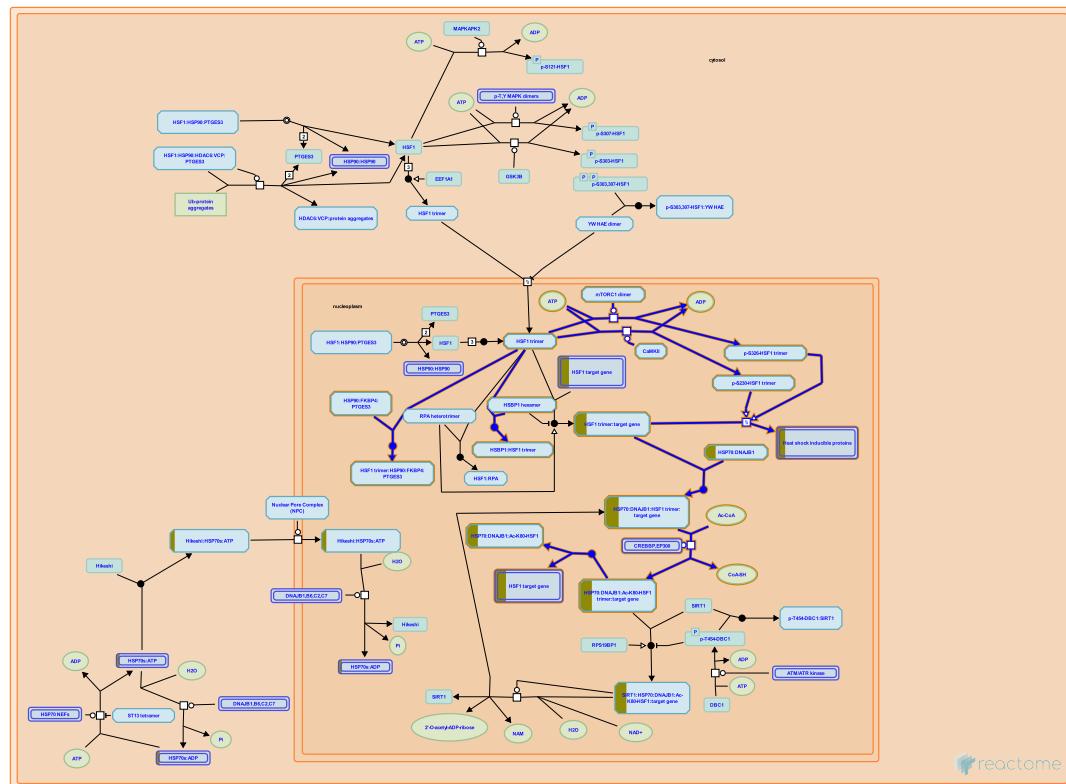
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2010-08-25	Created	Shamovsky V
2010-11-15	Edited	Shamovsky V
2010-11-30	Reviewed	Gillespie ME

Date	Action	Author
2012-11-13	Reviewed	Fitzgerald KA
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
IKBKB	O14920	UBB	P0CG47, P62979, P62987

## 21. HSF1-dependent transactivation (R-HSA-3371571)



Acquisition of DNA binding activity by HSF1 is necessary but insufficient for transcriptional activation (Cotto JJ et al. 1996; Trinklein ND et al. 2004). In addition to having a sequence-specific DNA binding domain, HSF1 contains a C-terminal region which is involved in activating the transcription of the target genes (Green M et al. 1995). However, the transactivating ability of the transactivation domain itself is not stress sensitive. Rather, it's controlled by a regulatory domain of HSF1 (amino acids 221-310), which represses the transactivating ability under normal physiological conditions (Green M et al. 1995; Zuo J et al. 1995; Newton EM et al. 1996). The HSF1 transactivation domain can be divided into two distinct regions, activation domain 1 (AD1) and activation domain 2 (AD2) (Brown SA et al. 1998). AD1 and AD2 each contain residues that are important for both transcriptional initiation and elongation. Mutations in acidic residues in both AD1 and AD2 preferentially affect the ability of HSF1 to stimulate transcriptional initiation, while mutations in phenylalanine residues preferentially affect stimulation of elongation (Brown SA et al. 1998).

Activation of the DNA-bound but transcriptionally incompetent HSF1 is thought to occur upon stress induced HSF1 phosphorylation at several serine residues (Ding XZ et al. 1997; Holmberg CI et al. 2001; Guettouche T et al. 2005). In cells exposed to heat, acquisition of HSE DNA-binding activity was observed to precede phosphorylation of HSF1 (Cotto JJ et al. 1996; Kline MP & Morimoto RI 1997). While there is a sufficient evidence to suggest that phosphorylation of HSF1 is essential to modulate HSF1 transactivating capacity, mechanisms behind stress stimuli and kinases/phosphatases involved have not been clearly established.

## References

Rungger D, Voellmy R & Zuo J (1995). Multiple layers of regulation of human heat shock transcription factor 1. Mol. Cell. Biol., 15, 4319-30. [View](#)

## Edit history

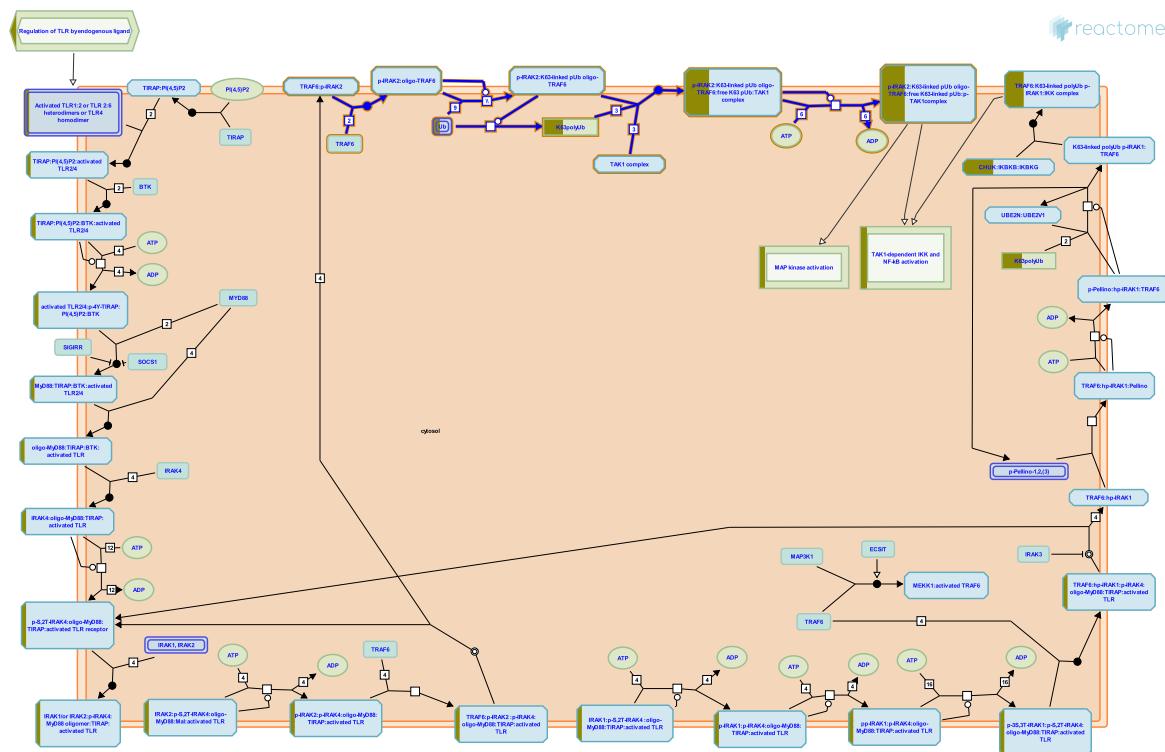
Date	Action	Author
2013-05-13	Created	Shamovsky V
2013-10-29	Authored	Shamovsky V
2014-02-17	Edited	Shamovsky V
2014-02-17	Reviewed	Pani B
2021-11-28	Modified	Weiser JD

## 2 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id
HSPA1L	P34931

Input	Ensembl Id	Input	Ensembl Id
HSPA1L	ENSG00000206383, ENSG00000226704, ENSG00000234258, ENSG00000236251	UBB	ENSG00000170315

## 22. IRAK2 mediated activation of TAK1 complex (R-HSA-937042)



**Cellular compartments:** plasma membrane, cytosol.

Although IRAK-1 was originally thought to be a key mediator of TRAF6 activation in the IL1R/TLR signaling (Dong W et al. 2006), recent studies showed that IRAK-2, but not IRAK-1, led to TRAF6 polyubiquitination (Keating SE et al 2007). IRAK-2 loss-of-function mutants, with mutated TRAF6-binding motifs, could no longer activate NF- $\kappa$ B and could no longer stimulate TRAF-6 ubiquitination (Keating SE et al 2007). Furthermore, the proxyvirus protein A52 - an inhibitor of all IL-1R/TLR pathways to NF- $\kappa$ B activation, was found to interact with both IRAK-2 and TRAF6, but not IRAK-1. Further work showed that A52 inhibits IRAK-2 functions, whereas association with TRAF6 results in A52-induced MAPK activation. The strong inhibition effect of A52 was also observed on the TLR3-NF $\kappa$ B axis and this observation led to the discovery that IRAK-2 is recruited to TLR3 to activate NF- $\kappa$ B (Keating SE et al 2007). Thus, A52 possibly inhibits MyD88-independent TLR3 pathways to NF- $\kappa$ B via targeting IRAK-2 as it does for other IL-1R/TLR pathways, although it remains unclear how IRAK-2 is involved in TLR3 signaling.

IRAK-2 was shown to have two TRAF6 binding motifs that are responsible for initiating TRAF6 signaling transduction (Ye H et al 2002).

## References

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Zou T, Liu Z, Liu Y, Xiao H, Peng J, Chen L, ... Li W (2006). The IRAK-1-BCL10-MALT1-TRAF6-TAK1 cascade mediates signaling to NF-kappaB from Toll-like receptor 4. *J Biol Chem*, 281, 26029-40.



Vologodskaya M, Kobayashi T, Wu H, Cirilli M, Lamothe B, Arron JR, ... Singh S (2002). Distinct molecular mechanism for initiating TRAF6 signalling. *Nature*, 418, 443-7.



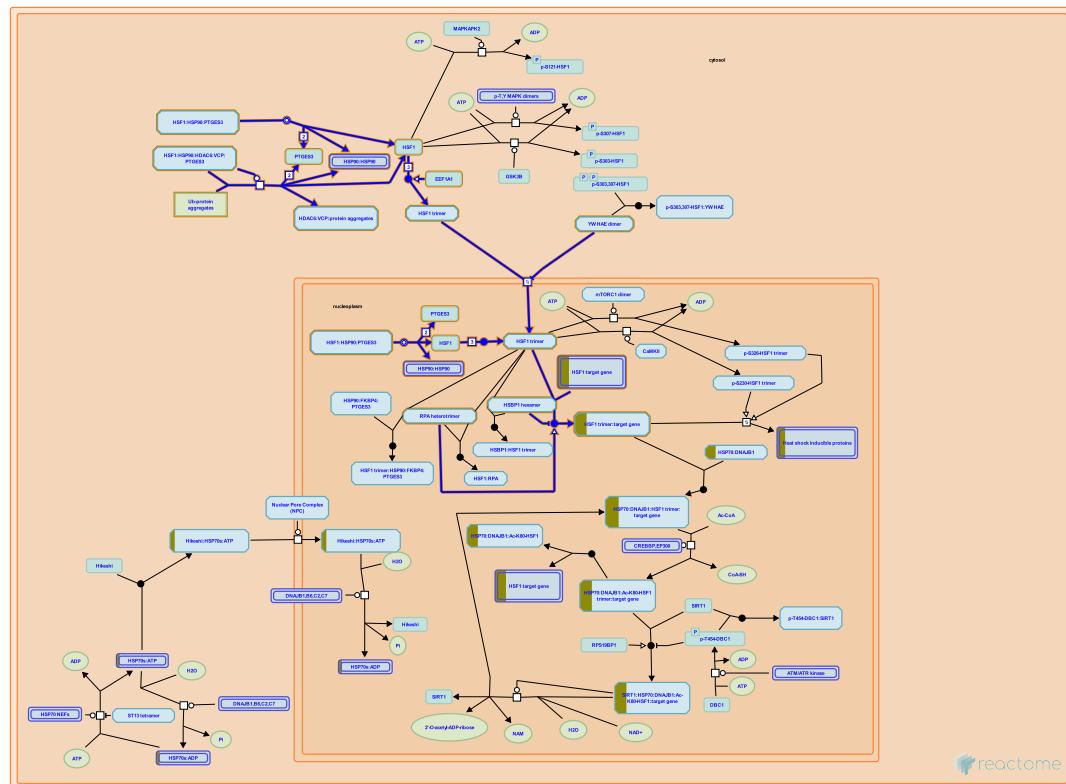
## Edit history

Date	Action	Author
2010-06-01	Authored	Shamovsky V
2010-08-25	Created	Shamovsky V
2010-11-30	Reviewed	Gillespie ME
2012-11-06	Edited	Shamovsky V
2012-11-16	Reviewed	Napetschnig J
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 23. HSF1 activation (R-HSA-3371511)



Heat shock factor 1 (HSF1) is a transcription factor that activates gene expression in response to a variety of stresses, including heat shock, oxidative stress, as well as inflammation and infection (Shamovsky I and Nudler E 2008; Akerfelt et al. 2010; Bjork and Sistonen 2010; Anckar and Sistonen 2011).

HSF1 is constitutively present in the cell. In the absence of stress HSF1 is found in both the cytoplasm and the nucleus as an inactive monomer (Sarge KD et al. 1993; Mercier PA et al. 1999; Vujanac M et al. 2005). A physical or chemical proteotoxic stress rapidly induces HSF1 activation, which occurs through a multi-step process, involving HSF1 monomer-to-homotrimer transition, nuclear accumulation, and binding to a promoter element, called the heat shock element (HSE), which leads to the increase in the stress-inducible gene expression (Sarge KD et al. 1993; Baler R et al. 1998; Sonna LA et al. 2002; Shamovsky I and Nudler E 2008; Sakurai H and Enoki Y 2010; Herbomel G et al. 2013). Depending on the type of stress stimulus, the multiple events associated with HSF1 activation might be affected differently (Holmberg CI et al 2000; Bjork and Sistonen 2010).

## References

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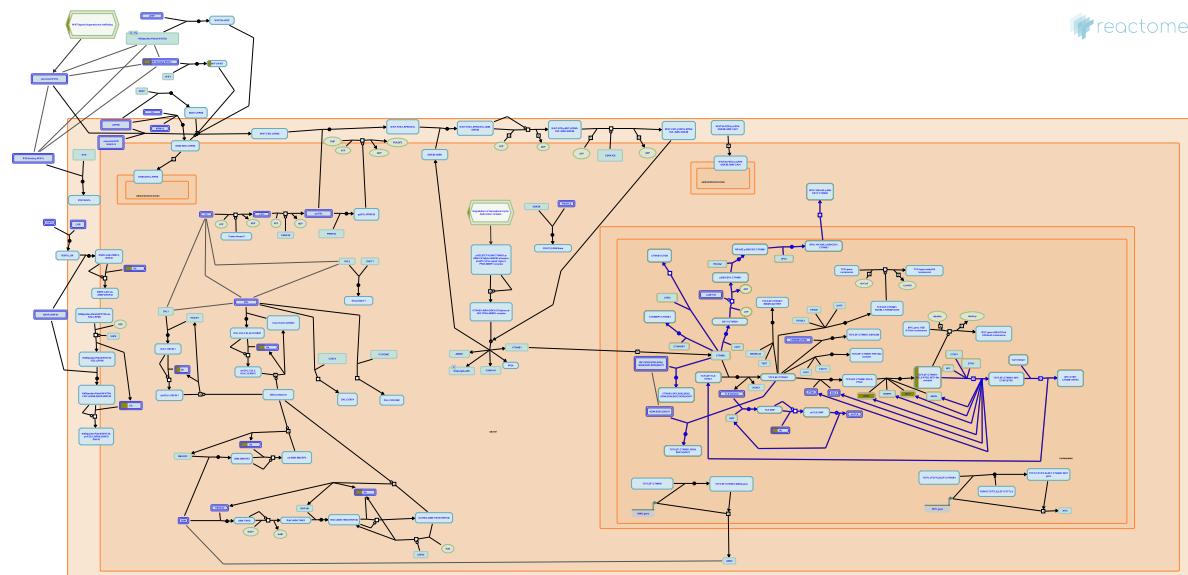
## Edit history

Date	Action	Author
2013-05-13	Created	Shamovsky V
2013-10-29	Authored	Shamovsky V
2014-02-17	Edited	Shamovsky V
2014-02-17	Reviewed	Pani B
2021-11-28	Modified	Weiser JD

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

Input	Ensembl Id	Input	Ensembl Id
HSPA1L	ENSG00000206383, ENSG00000226704, ENSG00000234258, ENSG00000236251	UBB	ENSG00000170315

## 24. Deactivation of the beta-catenin transactivating complex (R-HSA-3769402)



The mechanisms involved in downregulation of TCF-dependent transcription are not yet very well understood. beta-catenin is known to recruit a number of transcriptional repressors, including Reptin, SMRT and NCoR, to the TCF/LEF complex, allowing the transition from activation to repression (Bauer et al, 2000; Weiske et al, 2007; Song and Gelmann, 2008). CTNNBIP1 (also known as ICAT) and Chibby are inhibitors of TCF-dependent signaling that function by binding directly to beta-catenin and preventing interactions with critical components of the transactivation machinery (Takemaru et al, 2003; Li et al, 2008; Tago et al, 2000; Graham et al, 2002; Daniels and Weiss, 2002). Chibby additionally promotes the nuclear export of beta-catenin in conjunction with 14-3-3/YWHAZ proteins (Takemura et al, 2003; Li et al, 2008). A couple of recent studies have also suggested a role for nuclear APC in the disassembly of the beta-catenin activation complex (Hamada and Bienz, 2004; Sierra et al, 2006). It is worth noting that while some of the players involved in the disassembly of the beta-catenin transactivating complex are beginning to be worked out in vitro, the significance of their role in vivo is not yet fully understood, and some can be knocked out with little effect on endogenous WNT signaling (see for instance Voronina et al, 2009).

## References

- Yamaguchi S, Zhang Y, Moon RT, Takemaru K, Lee YS & Carthew RW (2003). Chibby, a nuclear beta-catenin-associated antagonist of the Wnt/Wingless pathway. *Nature*, 422, 905-9. [🔗](#)
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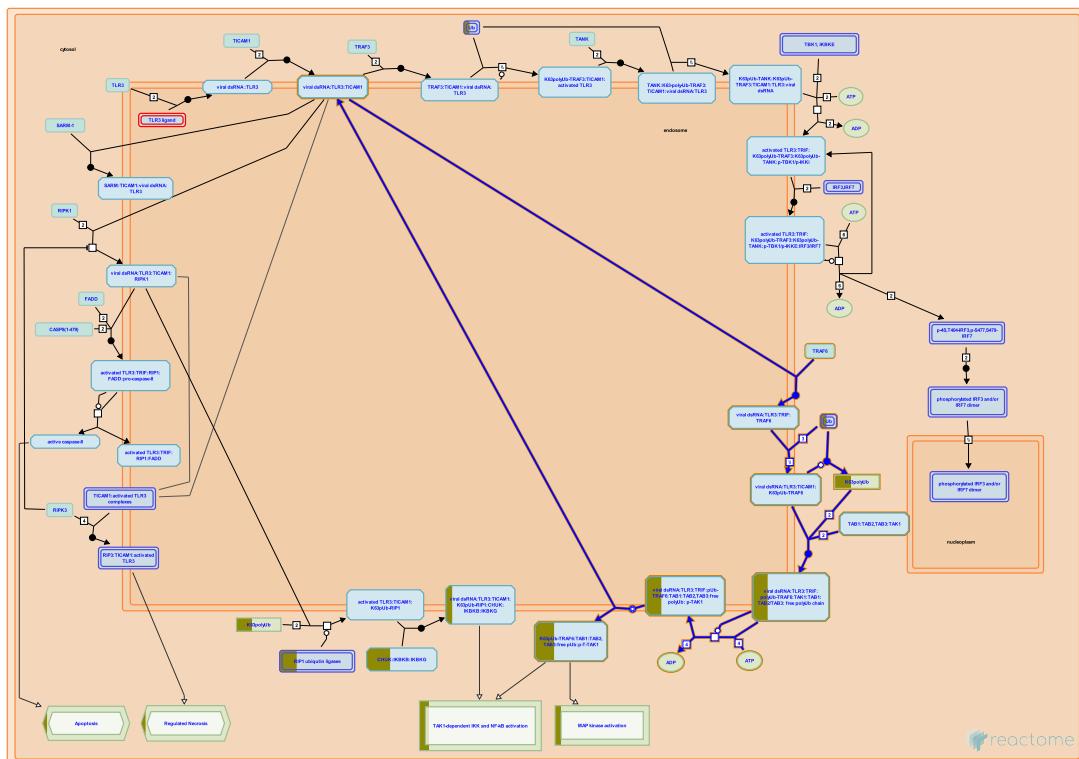
## Edit history

Date	Action	Author
2007-09-04	Edited	Matthews L
2013-05-30	Authored	Rothfels K
2013-06-20	Created	Rothfels K
2013-10-03	Edited	Gillespie ME
2014-01-22	Reviewed	Rajakulendran N
2014-02-15	Reviewed	van Amerongen R
2014-04-22	Reviewed	Kikuchi A
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
MLL2	O14686	MLL4	O14686
SCG2	O00255	UBB	P0CG47, P62979, P62987

## 25. TICAM1,TRAF6-dependent induction of TAK1 complex (R-HSA-9014325)



**Cellular compartments:** endosome membrane, cytosol.

In human, together with ubiquitin-conjugating E2-type enzymes UBC13 and UEV1A (also known as UBE2V1), TRAF6 catalyses Lys63-linked ubiquitination. It is believed that auto polyubiquitination and oligomerization of TRAF6 is followed by binding the ubiquitin receptors of TAB2 or TAB3 (TAK1 binding protein 2 and 3), which stimulates phosphorylation and activation of TGF beta-activated kinase 1(TAK1).

TAK1 phosphorylates IKK alpha and IKK beta, which in turn phosphorylate NF-κB inhibitors - IκB and eventually results in IκB degradation and NF-κB translocation to the nucleus. Also TAK1 mediates JNK and p38 MAP kinases activation by phosphorylating MKK4/7 and MKK3/6 respectively resulting in the activation of many transcription factors.

The role of TRAF6 is somewhat controversial and probably cell type specific. TRAF6 autoubiquitination was found to be dispensable for TRAF6 function to activate TAK1 pathway. These findings are consistent with the new mechanism of TRAF6-mediated NF-κB activation that was suggested by Xia et al. (2009). TRAF6 generates unanchored Lys63-linked polyubiquitin chains that bind to the regulatory subunits of TAK1 (TAB2 or TAB3) and IKK(NEMO), leading to the activation of the kinases.

Xia et al. (2009) demonstrated in vitro that unlike polyubiquitin chains covalently attached to TRAF6 or IRAK, TAB2 and NEMO-associated ubiquitin chains were found to be unanchored and susceptible to N-terminal ubiquitin cleavage. Only K63-linked polyubiquitin chains, but not monomeric ubiquitin, activated TAK1 in a dose-dependent manner. Optimal activation of the IKK complex was achieved using ubiquitin polymers containing both K48 and K63 linkages.

Furthermore, the authors proposed that the TAK1 complexes might be brought in close proximity by binding several TAB2/3 to a single polyubiquitin chain to facilitate TAK1 kinase trans-phosphorylation. Alternatively, the possibility that polyUb binding promotes allosteric activation of TAK1 complex should be considered (Walsh et al 2008).

## References

Adhikari A, Zeng W, Chen ZJ, Pineda G, Sun L, Chen X, ... Xia ZP (2009). Direct activation of protein kinases by unanchored polyubiquitin chains. *Nature*. [\[CrossRef\]](#)

Walsh MC, Molnar EE, Maurizio PL, Choi Y & Kim GK (2008). TRAF6 autoubiquitination-independent activation of the NF $\kappa$ B and MAPK pathways in response to IL-1 and RANKL. *PLoS One*, 3, e4064. [\[CrossRef\]](#)

## Edit history

Date	Action	Author
2010-06-01	Authored	Shamovsky V
2010-11-15	Edited	Shamovsky V
2010-11-30	Reviewed	Gillespie ME
2012-11-13	Reviewed	Fitzgerald KA
2017-07-28	Created	Shamovsky V
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 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.

**143 of the submitted entities were found, mapping to 194 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ADCY4	Q8NFM4	ADH1C	P00325, P00326, P07327	ANG	P03950
ANK2	Q01484	AQP12B	Q8IXF9	ATP13A1	Q9HD20
ATP6V1G2	O95670	ATP8A2	Q9NTI2	BRP44	O95563
C17orf79	Q9NQ92	CACNB2	Q08289	CAPNS1	P04632, Q96L46
CBX6	O95503	CECR1	Q9NZK5	CEP89	Q96ST8
CHST4	Q8NCG5	CLPS	P04118	CNGA1	P29973
COL10A1	Q03692	CPLX1	O14810	CPSF4	O95639
CTRC	Q99895	DDC	P20711	DGKQ	P52824
DOCK9	Q9BZ29	DSCAML1	Q8TD84	EPB41L3	Q9Y2J2
F13A1	P00488	FAM20C	Q8IXL6	FANCG	O15287
FASN	P49327	FBXW4	P57775	FBXW7	Q969H0-1, Q969H0-4
GABPB2	Q06547-1, Q06547-2, Q06547-3, Q06547-4	GATM	P50440	GCG	P01275
GNAS	P63092, Q5JWF2	GNB2	P62879	GPC6	Q9Y625
GRIA3	P42263	GSTA1	P08263	GSTA2	P09210
HAP1	P27695	HJURP	Q8NCD3	HLA-DMB	P28068
HLA-DQA1	P01909, P20036	HLA-DRB5	Q30154	HMGB2	P26583
HMGCS1	Q01581	HSPA1L	P34931	IKBKB	O14920
KCNH2	Q12809	KDM4B	O94953	KHDRBS3	O75525
KIF5C	O60282	KIRREL2	Q6UWL6	LSAMP	Q13449
LSM7	Q9UK45	MC1R	Q01726	MECP2	P51608-1, P51608-2
MED19	A0JLT2	MINK1	Q8N4C8	MLF1IP	Q71F23
MLL2	O14686	MLL4	O14686	MLXIPL	Q9NP71
MMP11	P24347	MMP15	P51511	MYLIP	Q8WY64
MZT2B	Q6NZ67	NEURL1B	A8MQ27	NFIL3	Q16649
NOL6	Q9H6R4	NPC1L1	Q9UHC9-2	NPHP4	O75161
ORM1	P02763	ORM2	P19652	PACSIN1	Q9BY11
PCSK2	P16519	PDCD7	Q8N8D1	PDPR	Q8NCN5
PEX7	O00628	PFDN5	Q99471	PHF16	Q92613
PI4KA	P42356	PKD1	P98161	PLXNA1	Q9UIW2
PLXNA3	P51805	PLXNB1	O43157	PNLIPRP1	P54315, P54317
PRKCH	P24723	PRSS1	P07477, P07478	PTTG1	O95997
PUS1	Q9Y606-1	PXMP2	Q9NR77	RANBP10	Q6VN20
RGL2	O15211	RGL3	Q3MIN7	RGNEF	Q8N1W1
RGS2	P41220	RNF144A	P50876	RNF217	Q8TC41
RPS4Y1	P22090, Q8TD47	RRP36	Q96EU6	S100Z	P05109, P80511
SALL4	Q9UJQ4	SCARB1	Q8WTV0-2	SCG2	O00255
SCN2A	P35498, Q15858, Q99250	SLC4A3	P48751	SLC6A19	Q695T7
SMPD1	P17405	SPG7	Q9UQ90	SRF	P11831

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
STK11IP	Q8N1F8	SUMF1	Q8NBK3	SYT7	O43581
TBC1D2	Q9BYX2	TBC1D20	Q96BZ9	TCTN1	Q2MV58
TESK1	Q15569	TK2	O00142	TRAPPC2L	Q9UL33
TTR	P02766	TUBGCP6	Q96RT7	TXNIP	Q9H3M7
UBB	P0CG47, P62979, P62987	UBOX5	O94941	USH1C	Q9Y6N9
VEGFB	P49765	VKORC1L1	Q8N0U8	WARS2	Q9UGM6
WDR59	Q6PJI9	WEE1	P30291, Q99640	WHSC1	O96028
WNK4	Q96J92	WNT4	O96014, P56705	ZNF211	Q13398
ZNF233	A6NK53, Q9NZL3	ZNF331	Q9NQX6	ZNF565	Q8N9K5
ZNF696	Q9H7X3	ZNF711	Q9Y462		

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
F13A1	ENSG00000124491	FASN	ENSG00000169710	GCG	ENSG00000115263
GSTA2	ENSG00000244067	HLA-DQA1	ENSG00000196735	HLA-DRB5	ENSG00000198502
HMGCS1	ENSG00000112972	HSPA1L	ENSG00000206383, ENSG00000226704, ENSG00000234258, ENSG00000236251	KDM4B	ENSG00000127663
MECP2	ENST00000303391, ENST00000453960	MINK1	ENSG00000141503	MYLIP	ENSG0000007944
SALL4	ENSG00000101115	UBB	ENSG00000170315	WNT4	ENSG00000162552

## 7. Identifiers not found

These 136 identifiers were not found neither mapped to any entity in Reactome.

ACAP3	AGPAT4-IT1	ANKHD1-EIF4EBP3	ANKRD26P1	BAI2	BMP8A	C10orf47	C11orf61
C12orf39	C15orf48	C17orf110	C19orf63	C1QTNF4	C1orf101	C1orf122	C4orf44
C5orf38	CACHD1	CALY	CAND2	CASKIN2	CBFA2T2	CCDC153	CCDC68
CCDC84	CDAN1	CDK2AP1	CDKN2B-AS1	CDYL2	CELSR3	CLEC1A	CMIP
CPA2	CPNE4	EIF4ENIF1	EML3	ERP27	FAIM2	FAM117A	FAM153C
FAM160A2	FAM185A	FDPSL2A	FEV	FRMPD1	GCNT2	GPR22	GPR6
GPR64	H6PD	HIC2	HTR7P1	HUNK	IQSEC1	ITM2A	KANSL1-AS1
KIAA0195	KIAA1161	KIAA1244	KIAA1324	LCN10	LETM2	LGALS2	LHFPL4
LOC100128568	LOC100130899	LOC100131434	LOC100505716	LOC283070	LOC344595	LOC553103	LOC643650
LOC643733	LOC645166	MAP3K9	MGC72080	MIR17HG	MIRLET7BHG	MSMB	NENF
NFE2L1	NFKBID	NME9	NRBP2	NUSAP1	PASK	PBOV1	PCDHB5
PCDHB7	PCDHGA7	PCP4	PGC	PHF10	PHF21B	PKI55	PLEKHH1
POSTN	PPP1R12C	PRRC2B	PTPRE	RBM24	RBM33	REG1A	RILPL2
SCG5	SEMA4G	SEPN1	SERPINI2	SETD5	SHISA7	SIX3	SLC10A3
SLIRP	SNX29	SPEF2	SPINK1	SSBP3	TARBP1	TMED6	TMEM41A
TMSB4Y	TNRC18	TPRG1L	TRAPPC2P1	TRY6	TSIX	TTC25	UBE4B
UNC119	USP27X	VSIG2	WDR66	ZBTB20-AS1	ZFR2	ZNF532	ZSWIM6