



# 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=MjAyMjAyMjYxNjA4MzRfMTc0MTI%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:

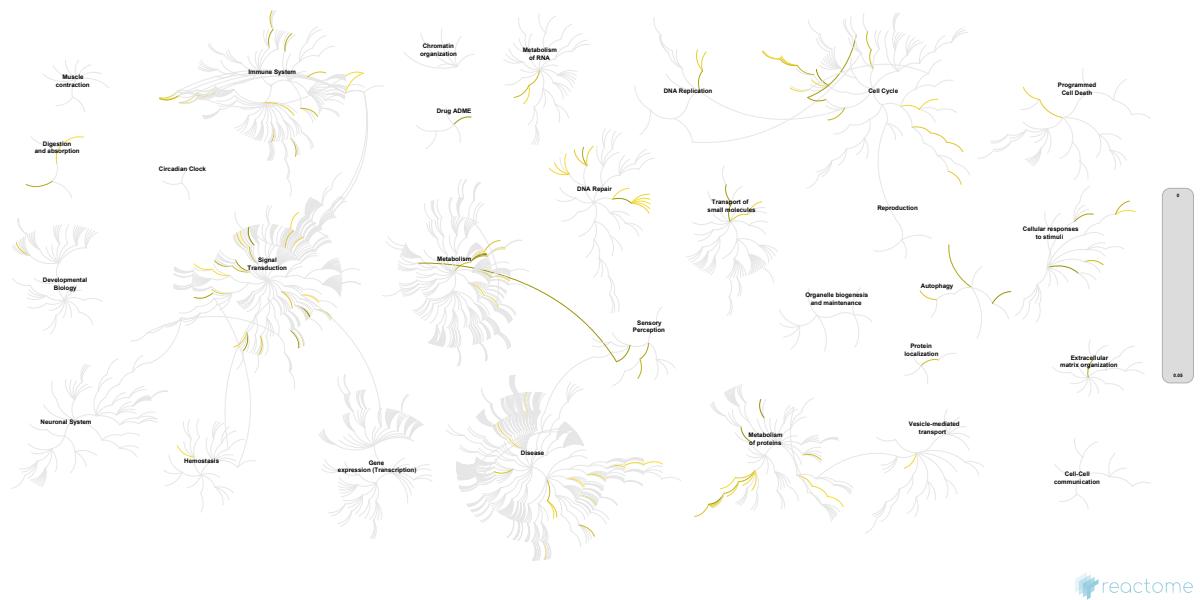
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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 Benjamani-Hochberg method. ↗
- 51 out of 67 identifiers in the sample were found in Reactome, where 827 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- IntAct interactors were included to increase the analysis background. This greatly increases the size of Reactome pathways, which maximises the chances of matching your submitted identifiers to the expanded pathway, but will include interactors that have not undergone manual curation by Reactome and may include interactors that have no biological significance, or unexplained relevance.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMjAyMjYxNjA4MzRfMTc0MTI%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
FLT3 signaling by CBL mutants	3 / 7	3.14e-04	8.06e-06	0.008	1 / 1	7.33e-05
Myoclonic epilepsy of Lafora	3 / 11	4.94e-04	3.08e-05	0.014	1 / 2	1.47e-04
Class B/2 (Secretin family receptors)	6 / 130	0.006	7.44e-05	0.023	6 / 20	0.001
Glucagon-type ligand receptors	4 / 50	0.002	1.59e-04	0.027	4 / 8	5.86e-04
Maturation of protein E	3 / 21	9.43e-04	2.06e-04	0.027	1 / 5	3.66e-04
Translesion synthesis by POLI	3 / 22	9.87e-04	2.36e-04	0.027	3 / 3	2.20e-04
Maturation of protein E	3 / 22	9.87e-04	2.36e-04	0.027	1 / 5	3.66e-04
Glycogen storage diseases	3 / 22	9.87e-04	2.36e-04	0.027	1 / 10	7.33e-04
Translesion synthesis by POLK	3 / 23	0.001	2.69e-04	0.028	3 / 3	2.20e-04
Glucagon signaling in metabolic regulation	4 / 59	0.003	2.97e-04	0.028	5 / 6	4.40e-04
Gap-filling DNA repair synthesis and ligation in GG-NER	3 / 27	0.001	4.28e-04	0.033	2 / 2	1.47e-04
Digestion of dietary lipid	3 / 27	0.001	4.28e-04	0.033	4 / 8	5.86e-04
Glucagon-like Peptide-1 (GLP1) regulates insulin secretion	4 / 69	0.003	5.33e-04	0.034	5 / 11	8.06e-04
Prostacyclin signalling through prostacyclin receptor	3 / 30	0.001	5.80e-04	0.034	3 / 4	2.93e-04
NOTCH2 Activation and Transmission of Signal to the Nucleus	3 / 31	0.001	6.38e-04	0.034	2 / 11	8.06e-04
Regulation of BACH1 activity	3 / 31	0.001	6.38e-04	0.034	1 / 7	5.13e-04
Membrane binding and targetting of GAG proteins	3 / 32	0.001	6.99e-04	0.034	3 / 4	2.93e-04
TGF-beta receptor signaling in EMT (epithelial to mesenchymal transition)	3 / 32	0.001	6.99e-04	0.034	2 / 6	4.40e-04
Synthesis And Processing Of GAG, GAGPOL Polyproteins	3 / 33	0.001	7.64e-04	0.034	3 / 5	3.66e-04
ER Quality Control Compartment (ERQC)	3 / 33	0.001	7.64e-04	0.034	2 / 9	6.60e-04
Glycogen synthesis	3 / 33	0.001	7.64e-04	0.034	2 / 24	0.002
APC-Cdc20 mediated degradation of Nek2A	3 / 34	0.002	8.32e-04	0.035	2 / 3	2.20e-04
Regulation of FZD by ubiquitination	3 / 35	0.002	9.04e-04	0.036	3 / 6	4.40e-04
InlB-mediated entry of Listeria monocytogenes into host cell	4 / 38	0.002	0.001	0.041	4 / 8	5.86e-04

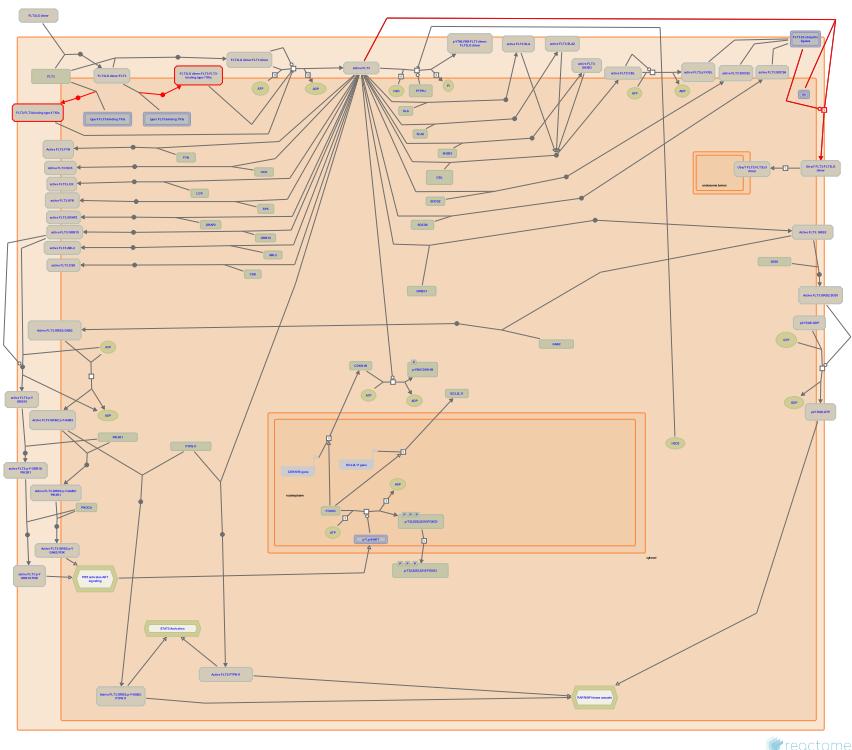
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Modulation by Mtb of host immune system	3 / 38	0.002	0.001	0.041	1 / 6	4.40e-04

\* 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. 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. 

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. 

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. 

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. 

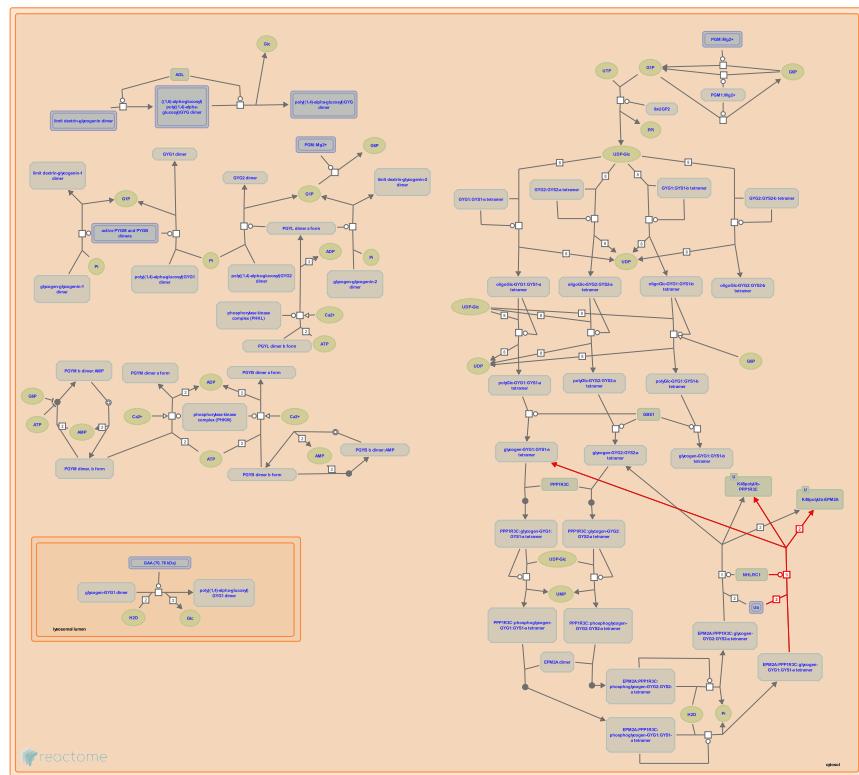
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2020-11-04	Created	Rothfels K
2020-11-06	Modified	Rothfels K
2020-11-06	Edited	Rothfels K
2020-11-06	Reviewed	Kazi JU
2020-11-06	Authored	Rothfels K

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 2. 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

- Piliguian M, Ackerley CA, Roach PJ, Cortez MA, Zhao X, Pencea N, ... Minassian BA (2011). PTG depletion removes Lafora bodies and rescues the fatal epilepsy of Lafora disease. PLoS Genet., 7, e1002037. [🔗](#)
- Gentry MS, Worby CA & Dixon JE (2005). Insights into Lafora disease: malin is an E3 ubiquitin ligase that ubiquitinates and promotes the degradation of laforin. Proc. Natl. Acad. Sci. U.S.A., 102, 8501-6. [🔗](#)
- Scherer SW, Jovic NJ, Chan EM, Avanzini G, Ackerley CA, Delgado-Escueta AV, ... Minassian BA (2003). Mutations in NHLRC1 cause progressive myoclonus epilepsy. Nat. Genet., 35, 125-7. [🔗](#)
- Epp JR, Ackerley CA, Roach PJ, Frankland P, Zhao X, Pencea N, ... Minassian BA (2013). Inhibiting glycogen synthesis prevents lafora disease in a mouse model. Ann. Neurol.. [🔗](#)
- Michelucci R, Gallardo ME, de Cerdoba SR, Tassinari CA, Dravet C, Malafosse A, ... Topcu M (1999). A novel protein tyrosine phosphatase gene is mutated in progressive myoclonus epilepsy of the Lafora type (EPM2). Hum. Mol. Genet., 8, 345-52. [🔗](#)

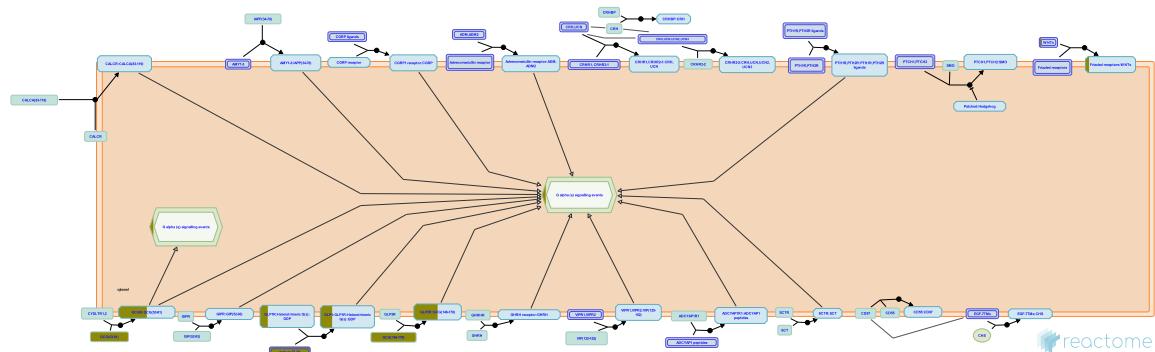
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2013-07-02	Created	D'Eustachio P
2013-07-19	Edited	D'Eustachio P
2013-07-19	Authored	D'Eustachio P
2014-02-19	Reviewed	Pederson B
2020-07-22	Modified	D'Eustachio P

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

### 3. Class B/2 (Secretin family receptors) (R-HSA-373080)



This family is known as Family B (secretin-receptor family, family 2) G-protein-coupled receptors. Family B GPCRs include secretin, calcitonin, parathyroid hormone/parathyroid hormone-related peptides and vasoactive intestinal peptide receptors; all of which activate adenylyl cyclase and the phosphatidyl-inositol-calcium pathway (Harmar AJ, 2001).

## References

Harmar AJ (2001). Family-B G-protein-coupled receptors. *Genome Biol*, 2, REVIEWS3013. 

## Edit history

Date	Action	Author
2008-07-14	Edited	Jassal B
2008-07-14	Authored	Jassal B
2008-07-14	Created	Jassal B
2009-05-29	Reviewed	D'Eustachio P
2021-11-27	Modified	Weiser JD

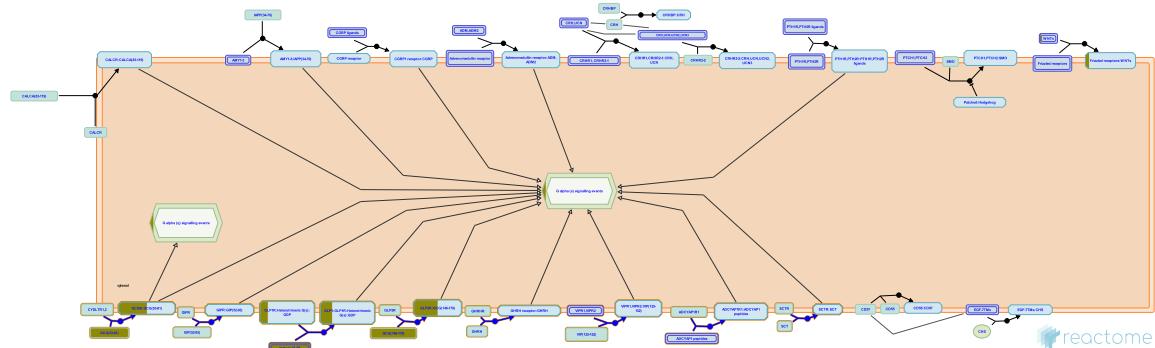
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GCG	P01275	GNAS	P63092, Q5JWF2
GNB2	P62879	WNT4	O96014, P56705

## Interactors found in this pathway (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
GCG	P01275	P01275, P48546	GNAS	P63092	P30988

#### 4. Glucagon-type ligand receptors (R-HSA-420092)



The glucagon hormone family regulates the activity of GPCRs from the secretin receptor subfamily in Class II/B (Mayo KE et al, 2003).

#### References

Miller LJ, Thorens B, Drucker DJ, GÃ¶ke B, Mayo KE, Dalle S & Bataille D (2003). International Union of Pharmacology. XXXV. The glucagon receptor family. *Pharmacol Rev*, 55, 167-94. [View](#)

#### Edit history

Date	Action	Author
2009-05-11	Edited	Jassal B
2009-05-11	Authored	Jassal B
2009-05-11	Created	Jassal B
2009-05-29	Reviewed	D'Eustachio P
2021-11-26	Modified	Weiser JD

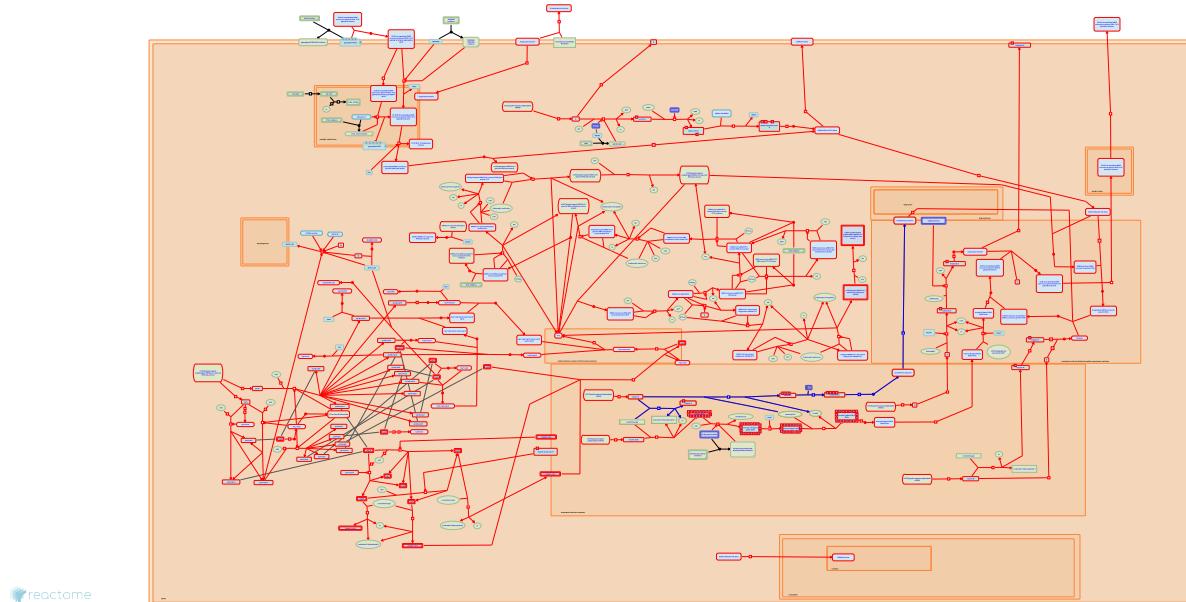
3 submitted entities found in this pathway, mapping to 4 Reactome entities

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

#### Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
GCG	P01275	P01275, P48546			

## 5. 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. [🔗](#)

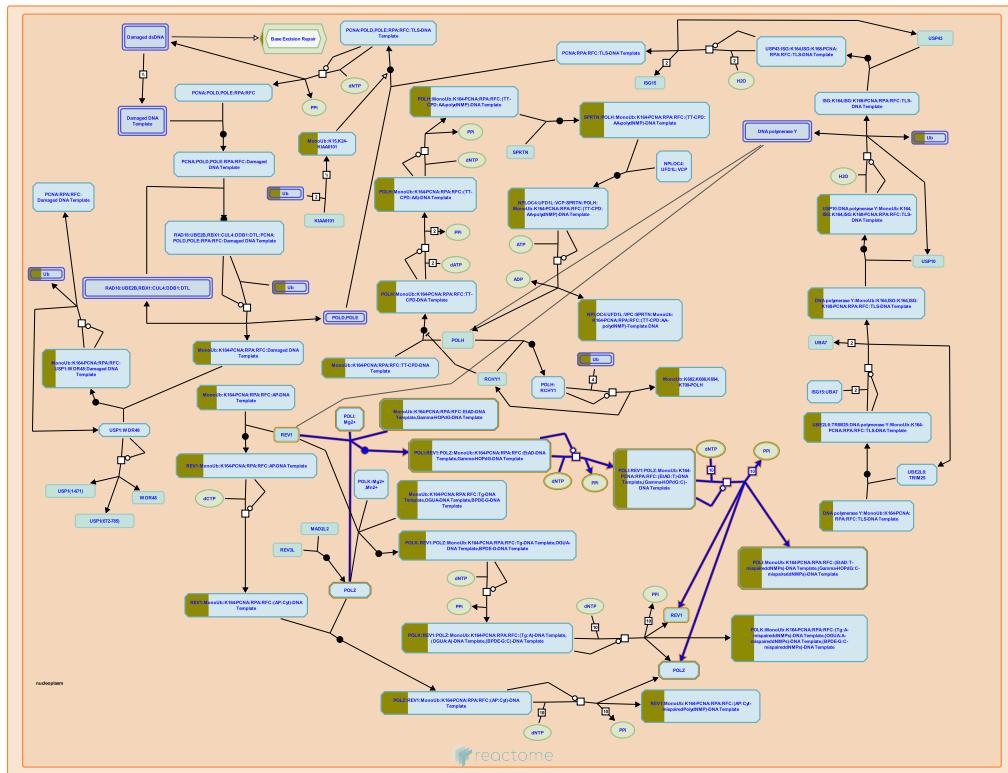
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Date	Action	Author
2020-04-08	Authored	Stephan R
2020-04-17	Created	Stephan R
2020-05-21	Edited	D'Eustachio P
2020-05-27	Reviewed	Mazein A, Acencio ML
2020-08-04	Modified	Gillespie ME

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 6. Translesion synthesis by POLI (R-HSA-5656121)



**Cellular compartments:** nucleoplasm.

DNA polymerase iota (POLI) is a Y family DNA polymerase with an active site that favours Hoogsteen base pairing instead of Watson-Crick base pairing. POLI-mediated Hoogsteen base pairing and rotation of template purines from anti to syn conformation serves as a mechanism to displace adducts on template G or template A that interfere with DNA replication, or to allow base pairing of damaged purines with a disrupted Watson-Crick edge but an intact Hoogsteen edge (Nair et al. 2004, Nair et al. 2006).

POLI is recruited to DNA damage sites through its interaction with PCNA and REV1. POLI contains a PIP box and two UBMs (ubiquitin binding motifs) that are responsible for POLI binding to mono-ubiquitinated PCNA (MonoUb:K164-PCNA) (Bienko et al. 2005, Haracska et al. 2005, Bomar et al. 2010). The interaction between POLI and the C-terminus of REV1 is evolutionarily conserved (Kosarek et al. 2003, Guo et al. 2003, Ohashi et al. 2004).

After it incorporates a dNMP opposite to damaged template base, POLI is unable to efficiently elongate the DNA strand further. The elongation step is performed by the polymerase zeta complex (POLZ), composed of REV3L and MAD2L2 subunits (Johnson et al. 2000). The involvement of REV1 and POLZ in POLI-mediated translesion DNA synthesis (TLS) suggests that POLI forms a quaternary complex with REV1 and POLZ, as shown for POLK and proposed for other Y family DNA polymerases (Xie et al. 2012).

## References

- Johnson RE, Haracska L, Washington MT, Prakash L & Prakash S (2000). Eukaryotic polymerases iota and zeta act sequentially to bypass DNA lesions. *Nature*, 406, 1015-9. [\[link\]](#)

Murakumo Y, Akagi J, Kanjo N, Hanaoka F, Ohmori H, Ohashi E & Masutani C (2004). Interaction of hREV1 with three human Y-family DNA polymerases. *Genes Cells*, 9, 523-31. [🔗](#)

Masuda Y, Friedberg EC, Zhou J, Fischhaber PL, Guo C, Kamiya K, ... Luk-Paszyc MJ (2003). Mouse Rev1 protein interacts with multiple DNA polymerases involved in translesion DNA synthesis. *EMBO J.*, 22, 6621-30. [🔗](#)

Xu M, Yang X, Xie W & Jiang T (2012). Structural insights into the assembly of human translesion polymerase complexes. *Protein Cell*, 3, 864-74. [🔗](#)

Johnson RE, Haracska L, Hurwitz J, Acharya N, Prakash L, Unk I & Prakash S (2005). A single domain in human DNA polymerase iota mediates interaction with PCNA: implications for translesion DNA synthesis. *Mol. Cell. Biol.*, 25, 1183-90. [🔗](#)

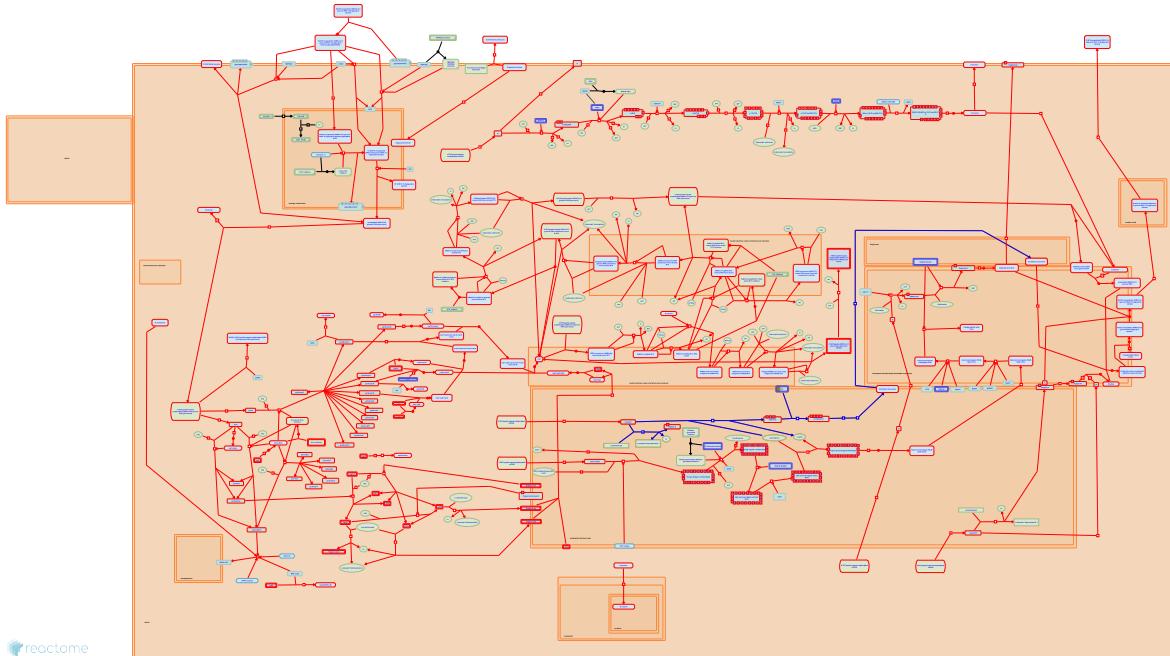
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2014-12-10	Created	Orlic-Milacic M
2014-12-11	Edited	Orlic-Milacic M
2014-12-11	Authored	Orlic-Milacic M
2015-01-07	Reviewed	Borowiec JA
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 7. 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. [🔗](#)

### Edit history

Date	Action	Author
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

## 8. Glycogen storage diseases (R-HSA-3229121)



**Diseases:** glycogen storage disease.

The regulated turnover of glycogen plays a central, tissue-specific role in the maintenance of blood glucose levels and in the provision of glucose to tissues such as muscle and brain in response to stress. Defects in the enzymes involved in glycogen turnover are associated with abnormal responses to fasting and exercise that can differ widely in their presentation and severity. Additional symptoms can be the result of accumulation of abnormal products of glycogen metabolism (Hauk et al. 1959; Hers 1964; Shin 2006). Annotations are provided here for diseases due to deficiencies of GYS1 and GYS1 (glycogen synthase 1 and 2; glycogen storage disease type 0 (GSD type 0), of G6PC (glucose-6-phosphatase, GSD type Ia) and the SLC37A4 transporter (GSD type Ib), of GAA (lysosomal acid alpha-glucosidase, GSD type II), of GBE1 (glycogen branching enzyme, GSD type IV), and of GYG1 (glycogenin 1, GSD XV). Two additional diseases, myoclonic epilepsy of Lafora (Roach et al. 2012) and severe congenital neutropenia type 4 (Bozta et al. 2009), are included as they are due to defects in enzymes of glycogen metabolism.

## References

- Klein C, Kratz C, Salzer U, Brandes G, Münkemüller K, Germeshausen M, ... Ashikov A (2009). A syndrome with congenital neutropenia and mutations in G6PC3. *N. Engl. J. Med.*, 360, 32-43. [🔗](#)
- Cori CF, Hauk R, Illingworth B & Brown DH (1959). Enzymes of glycogen synthesis in glycogen-deposition disease. *Biochim. Biophys. Acta*, 33, 554-6. [🔗](#)
- Hers HG (1964). Glycogen storage disease. *Adv Metab Disord*, 13, 1-44. [🔗](#)
- Shin YS (2006). Glycogen storage disease: clinical, biochemical, and molecular heterogeneity. *Semin Pediatr Neurol*, 13, 115-20. [🔗](#)

Hurley TD, Roach PJ, Tagliabracci VS & DePaoli-Roach AA (2012). Glycogen and its metabolism: some new developments and old themes. Biochem. J., 441, 763-87. [🔗](#)

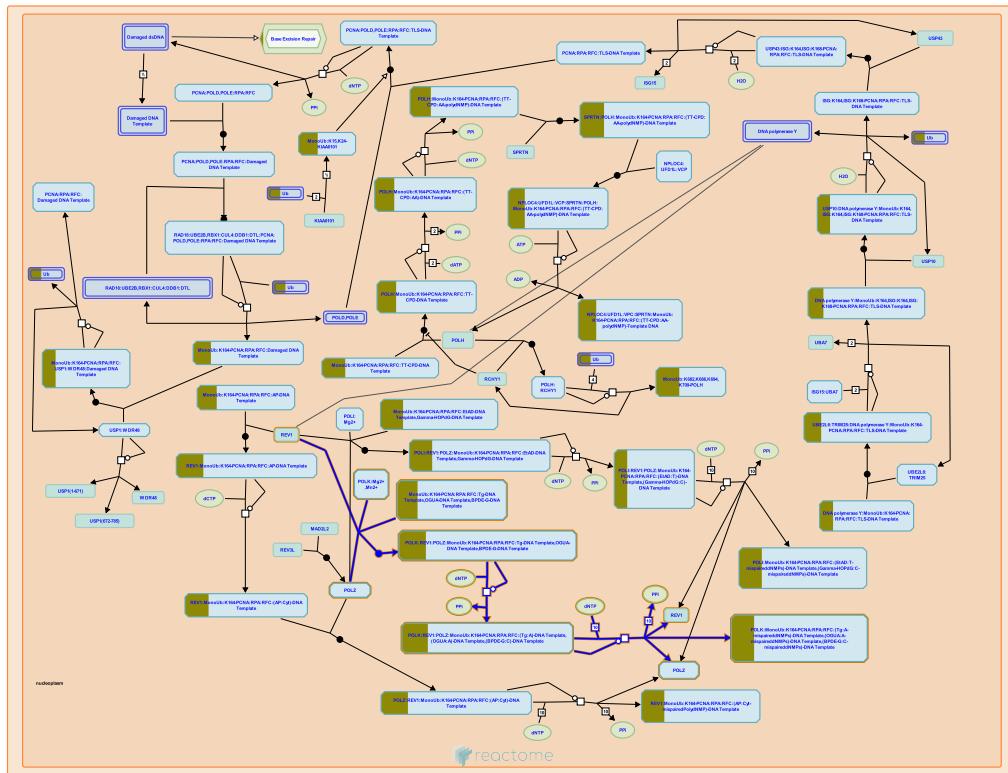
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2013-07-19	Edited	D'Eustachio P
2013-07-19	Authored	D'Eustachio P
2015-08-17	Modified	D'Eustachio P
2015-08-17	Reviewed	Jassal B

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 9. Translesion synthesis by POLK (R-HSA-5655862)



**Cellular compartments:** nucleoplasm.

DNA polymerase kappa (POLK) is a Y family DNA polymerase that is most efficient in translesion DNA synthesis (TLS) across oxidation derivatives of DNA bases, such as thymine glycol (Tg) and 8-oxoguanine (OGUA), as well as bulky DNA adducts, such as benzo(a)pyrene diol epoxide guanine adduct (BPDE-G) (Zhang et al. 2000, Fischhaber et al. 2002, Avkin et al. 2004, Vasquez-Del Carpio et al. 2009, Yoon et al. 2010, Lior-Hoffmann et al. 2012, Christov et al. 2012, Yoon et al. 2014). POLK carries out TLS by forming a quaternary complex with REV1 and monoubiquitinated PCNA (Ohashi et al. 2009, Haracska, Unk et al. 2002, Bi et al. 2006). POLK and POLZ cooperate in the elongation of nucleotides inserted opposite to lesioned bases by POLK. Similarly to POLZ, POLK has low processivity and is error-prone (Ohashi et al. 2000, Haracska, Prakash et al. 2002, Yoon et al. 2010).

## References

- Prakash L, Roy Choudhury J, Yoon JH, Park J & Prakash S (2014). A role for DNA polymerase ? in promoting replication through oxidative DNA lesion, thymine glycol, in human cells. *J. Biol. Chem.*, 289, 13177-85. [🔗](#)
- Geacintov NE, Zhang Y, Yuan F, Wang M, Taylor JS, Wang Z, ... Wu X (2000). Error-free and error-prone lesion bypass by human DNA polymerase kappa in vitro. *Nucleic Acids Res.*, 28, 4138-46. [🔗](#)
- Gerlach VL, Feaver WJ, Friedberg EC, Kunkel TA, Matsuda T, Ohashi E, ... Ohmori H (2000). Fidelity and processivity of DNA synthesis by DNA polymerase kappa, the product of the human DINB1 gene. *J. Biol. Chem.*, 275, 39678-84. [🔗](#)

Hatahet Z, Friedberg EC, Gerlach VL, Fischhaber PL, Feaver WJ & Wallace SS (2002). Human DNA polymerase kappa bypasses and extends beyond thymine glycols during translesion synthesis in vitro, preferentially incorporating correct nucleotides. *J. Biol. Chem.*, 277, 37604-11. ↗

Rizzo CJ, Christov PP, Lloyd RS, Wood RD, Takata K, Choi JY, ... Yamanaka K (2012). Replication of the 2,6-diamino-4-hydroxy-N(5)-(methyl)-formamidopyrimidine (MeFapy-dGuo) adduct by eukaryotic DNA polymerases. *Chem. Res. Toxicol.*, 25, 1652-61. ↗

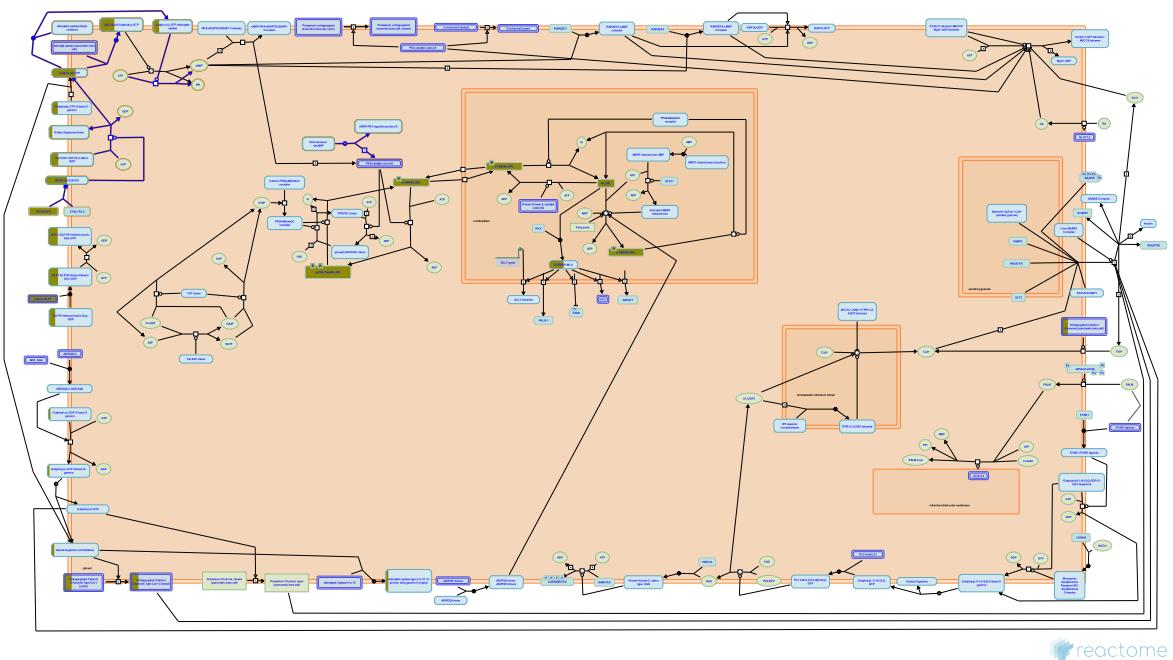
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2014-12-11	Edited	Orlic-Milacic M
2014-12-11	Authored	Orlic-Milacic M
2015-01-07	Reviewed	Borowiec JA
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 10. 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

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

### Edit history

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

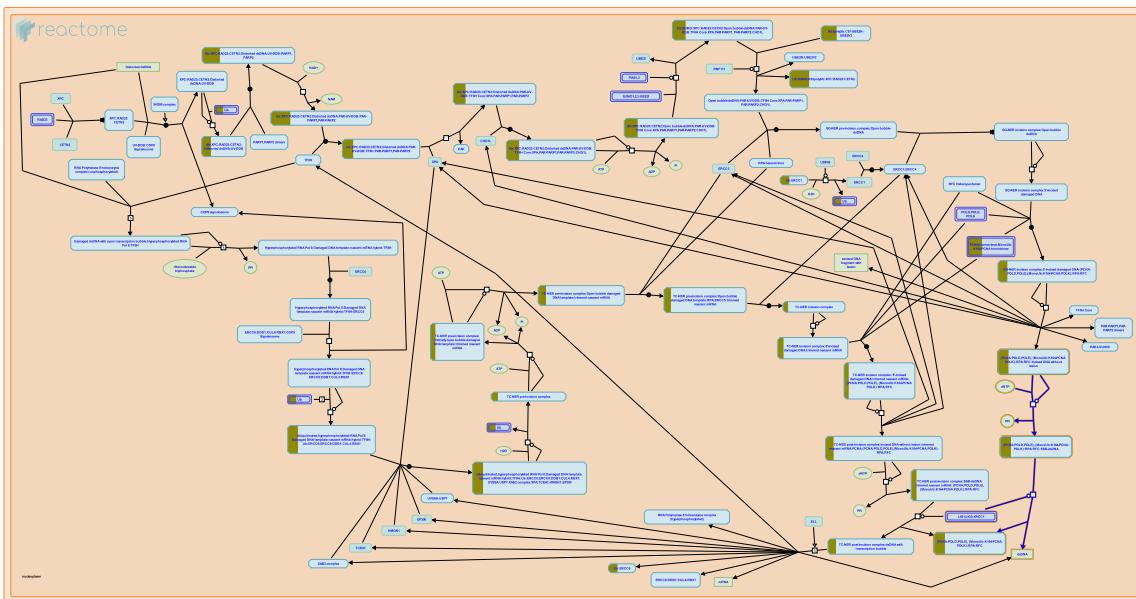
3 submitted entities found in this pathway, mapping to 4 Reactome entities

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GCG	P01275	GNAS	P63092, Q5JWF2	GNB2	P62879

### Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
GCG	P01275	P01275			

## 11. Gap-filling DNA repair synthesis and ligation in GG-NER (R-HSA-5696397)



**Cellular compartments:** nucleoplasm.

Global genome nucleotide excision repair (GG-NER) is completed by DNA repair synthesis that fills the single stranded gap created after dual incision of the damaged DNA strand and excision of the ~27-30 bases long oligonucleotide that contains the lesion. DNA synthesis is performed by DNA polymerases epsilon or delta, or the Y family DNA polymerase kappa (POLK), which are loaded to the repair site after 5' incision (Staresinic et al. 2009, Ogi et al. 2010). DNA ligases LIG1 or LIG3 (as part of the LIG3:XRCC1 complex) ligate the newly synthesized stretch of oligonucleotides to the incised DNA strand (Moser et al. 2007).

## References

- Limsirichaikul S, Takenaka K, Yamashita S, Cloney R, Lehmann AR, Miki Y, ... Nakazawa Y (2010). Three DNA polymerases, recruited by different mechanisms, carry out NER repair synthesis in human cells. *Mol. Cell*, 37, 714-27. [🔗](#)
- Wijgers N, Staresinic L, Schärer OD, Gourdin AM, Fagbemi AF, Enzlin JH, ... Vermeulen W (2009). Coordination of dual incision and repair synthesis in human nucleotide excision repair. *EMBO J.*, 28, 1111-20. [🔗](#)
- Fousteri M, Mullenders LH, Giakzidis I, Moser J, Caldecott K & Kool H (2007). Sealing of chromosomal DNA nicks during nucleotide excision repair requires XRCC1 and DNA ligase III alpha in a cell-cycle-specific manner. *Mol. Cell*, 27, 311-23. [🔗](#)

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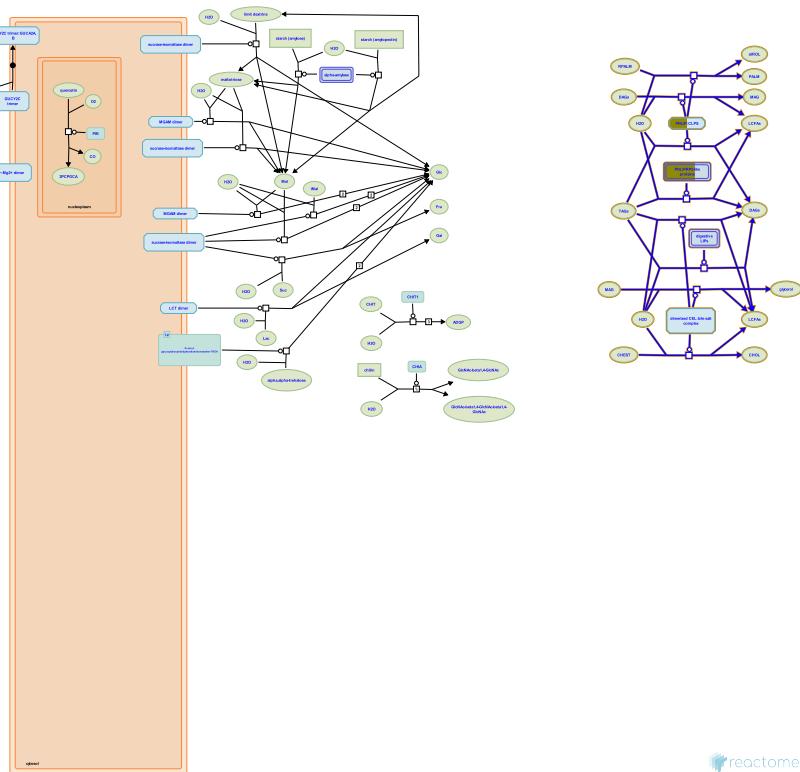
Date	Action	Author
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2004-02-02	Authored	Gopinathrao G
2015-05-29	Created	Orlic-Milacic M
2015-06-16	Revised	Orlic-Milacic M
2015-06-16	Edited	Orlic-Milacic M

Date	Action	Author
2015-06-16	Authored	Orlic-Milacic M
2015-08-03	Reviewed	Fousteri 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

## 12. Digestion of dietary lipid (R-HSA-192456)



### **Cellular compartments: extracellular region.**

Dietary lipids such as long-chain triacylglycerols and cholesterol esters are digested in the stomach and small intestine to yield long-chain fatty acids, monoacylglycerols, glycerol and cholesterol through the action of a variety of lipases, and are then absorbed into enterocytes.

## References

Lombardo D (2001). Bile salt-dependent lipase: its pathophysiological implications. *Biochim Biophys Acta*, 1533, 1-28. 

Lowe ME (2002). The triglyceride lipases of the pancreas. *J Lipid Res*, 43, 2007-16. ↗

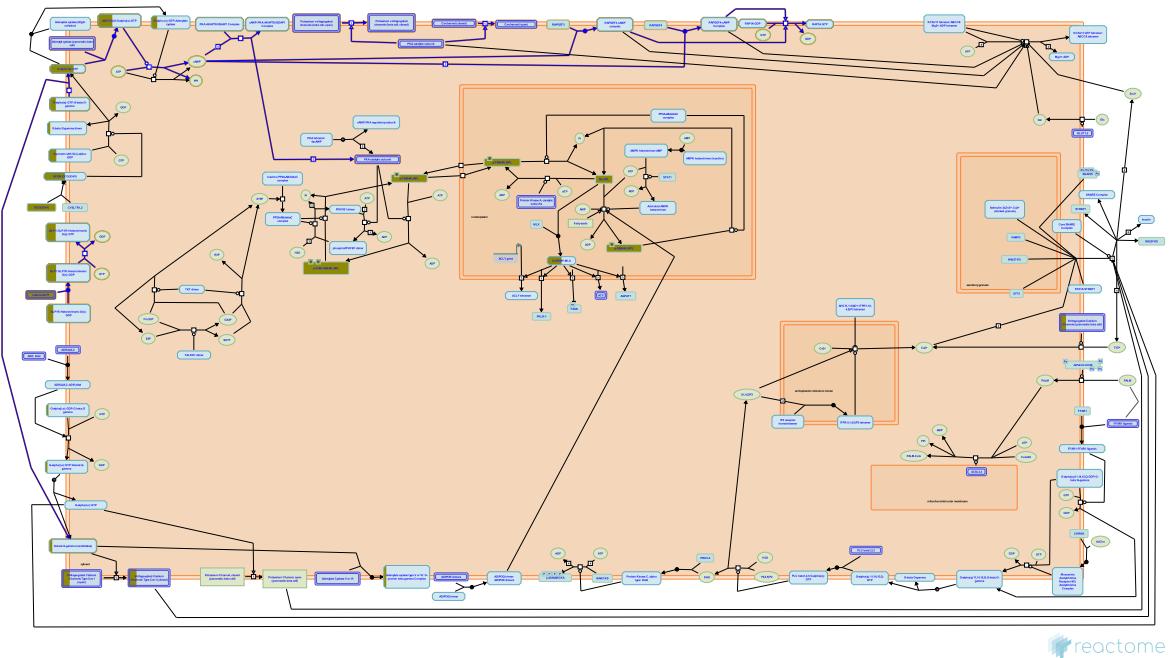
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2007-02-03	Authored	D'Eustachio P
2007-02-03	Created	D'Eustachio P
2021-11-28	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
CLPS	P04118	PNLIPRP1	P54315, P54317

### 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

- Gromada J & Rorsman P (1996). Molecular mechanism underlying glucagon-like peptide 1 induced calcium mobilization from internal stores in insulin-secreting beta TC3 cells. *Acta Physiol Scand*, 157, 349-51. [🔗](#)
- Brock B, Gromada J, Rorsman P & Schmitz O (2004). Glucagon-like peptide-1: regulation of insulin secretion and therapeutic potential. *Basic Clin Pharmacol Toxicol*, 95, 252-62. [🔗](#)
- Riedel MJ, Wheeler MB, MacDonald PE, Light PE, Salapatek AM & El-Kholy W (2002). The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. *Diabetes*, 51, S434-42. [🔗](#)
- Ahren B & Winzell MS (2007). G-protein-coupled receptors and islet function-implications for treatment of type 2 diabetes. *Pharmacol Ther*, 116, 437-48. [🔗](#)
- Lang J (1999). Molecular mechanisms and regulation of insulin exocytosis as a paradigm of endocrine secretion. *Eur J Biochem*, 259, 3-17. [🔗](#)

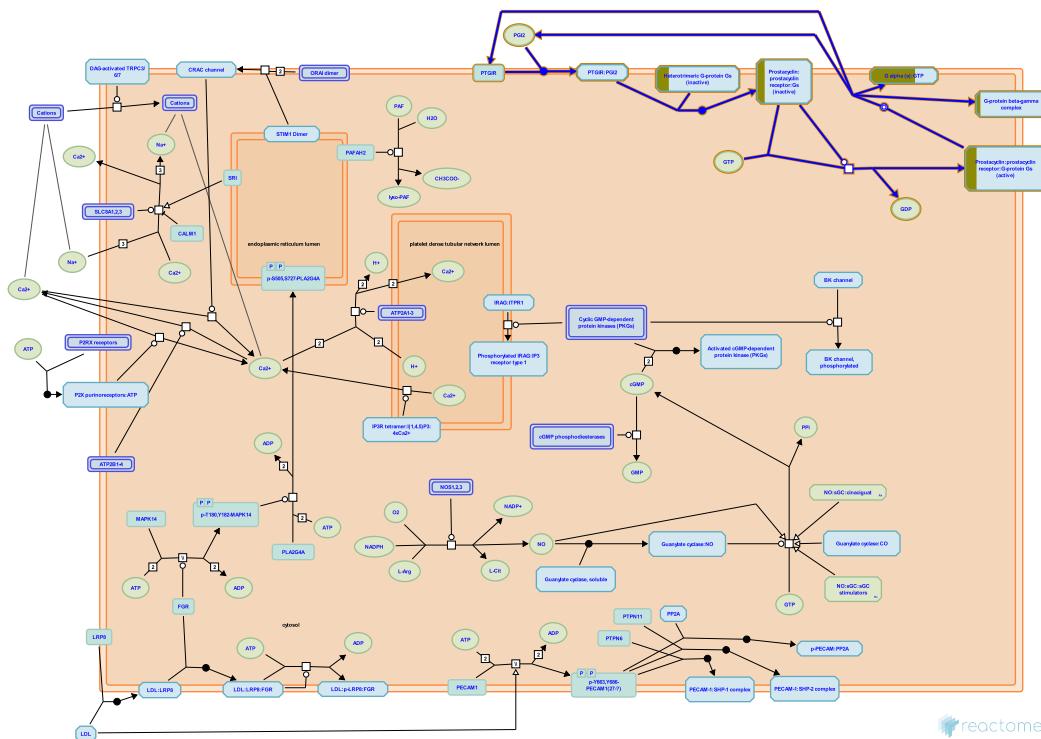
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2009-06-02	Reviewed	Gillespie ME
2021-11-28	Modified	Weiser JD

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

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

## 14. Prostacyclin signalling through prostacyclin receptor (R-HSA-392851)



**Cellular compartments:** plasma membrane.

Prostacyclin (PGI<sub>2</sub>) is continuously produced by healthy vascular endothelial cells. It inhibits platelet activation through interaction with the Gs-coupled receptor PTGIR, leading to increased cAMP, a consequent increase in cAMP-dependent protein kinase activity which prevents increases of cytoplasmic [Ca<sup>2+</sup>] necessary for activation (Woulfe et al. 2001). PGI<sub>2</sub> is also an effective vasodilator. These effects oppose the effects of thromboxane (TXA<sub>2</sub>), another eicosanoid, creating a balance of blood circulation and platelet activation.

## References

Douville KL, Stitham J, Arehart EJ, Hwa J & Gleim SR (2007). Human prostacyclin receptor structure and function from naturally-occurring and synthetic mutations. *Prostaglandins Other Lipid Mediat*, 82, 95-108. [View](#)

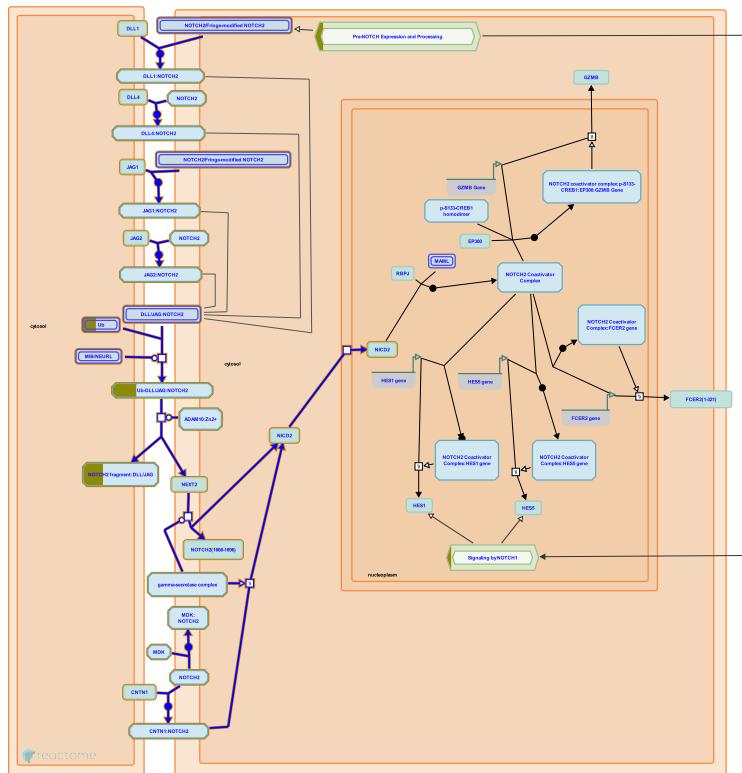
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2010-06-07	Edited	Jupe S
2010-06-07	Reviewed	Kunapuli SP
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id	Input	UniProt Id
GNAS	P63092, Q5JWF2	GNB2	P62879

## 15. 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

- Kanda Y, Kurokawa M, Shimizu K, Hirai H, Kumano K, Hamada Y, ... Hosoya N (2000). Binding of Delta1, Jagged1, and Jagged2 to Notch2 rapidly induces cleavage, nuclear translocation, and hyperphosphorylation of Notch2. *Mol Cell Biol*, 20, 6913-22. [🔗](#)
- Collazo A, Johnston SH, Hicks C, Weinmaster G, diSibio G & Vogt TF (2000). Fringe differentially modulates Jagged1 and Delta1 signalling through Notch1 and Notch2. *Nat Cell Biol*, 2, 515-20. [🔗](#)
- Saxena MT, Kopan R, Schroeter EH & Mumm JS (2001). Murine notch homologs (N1-4) undergo presenilin-dependent proteolysis. *J Biol Chem*, 276, 40268-73. [🔗](#)

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, Gómez 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. [🔗](#)

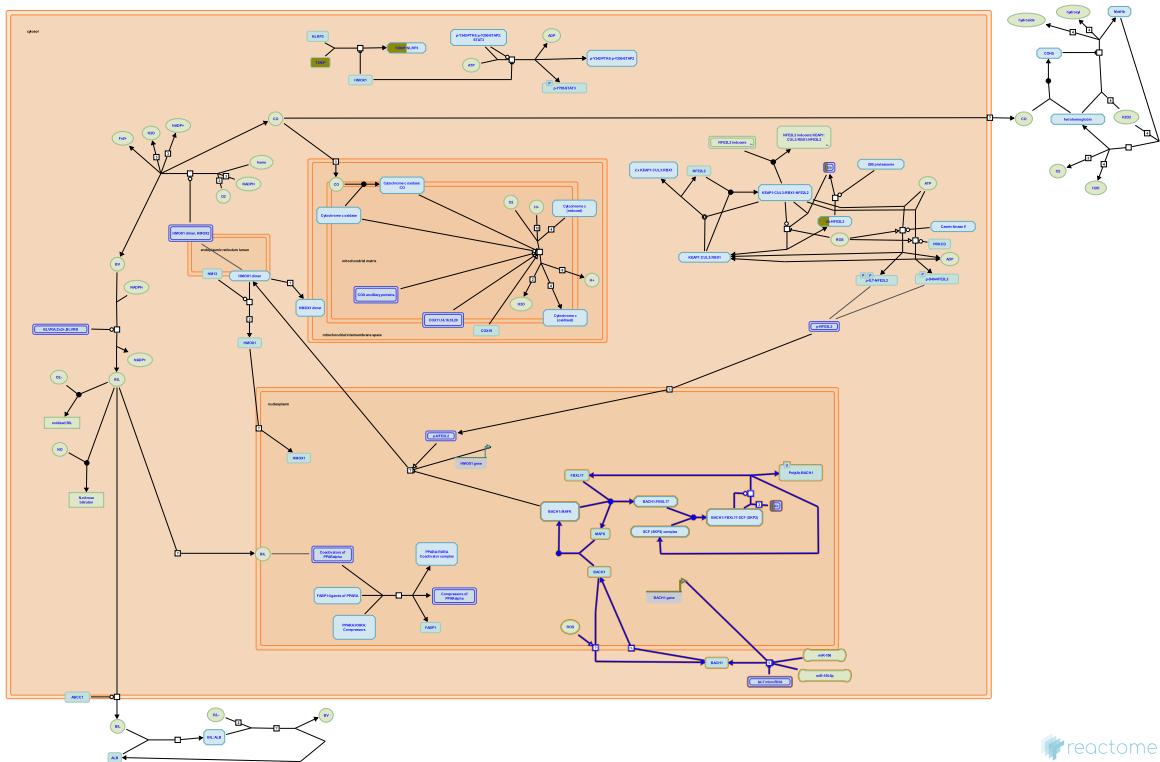
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2013-01-11	Created	Orlic-Milacic M
2013-01-14	Edited	Haw R
2013-04-25	Reviewed	Ilagan MXG, Boyle S
2021-11-26	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 16. Regulation of BACH1 activity (R-HSA-9708530)



**Cellular compartments:** cytosol.

The transcription factor BTB and CNC homology 1 (BACH1) is widely expressed in most mammalian tissues and functions primarily as a transcriptional suppressor by heterodimerizing with small Maf proteins and binding to Maf recognition elements in the promoters of targeted genes. It has a key regulatory role in the production of reactive oxygen species (ROS), cell cycle, heme homeostasis, hematopoiesis, and immunity and has been shown to suppress ischemic angiogenesis and promote breast cancer metastasis (Zhang et al, 2018; Okada et al, 2010).

## References

Jia M, Li Q, Meng D, Wei X, Niu C, Zhang X & Guo J (2018). Bach1: Function, Regulation, and Involvement in Disease. *Oxid Med Cell Longev*, 2018, 1347969. [View](#)

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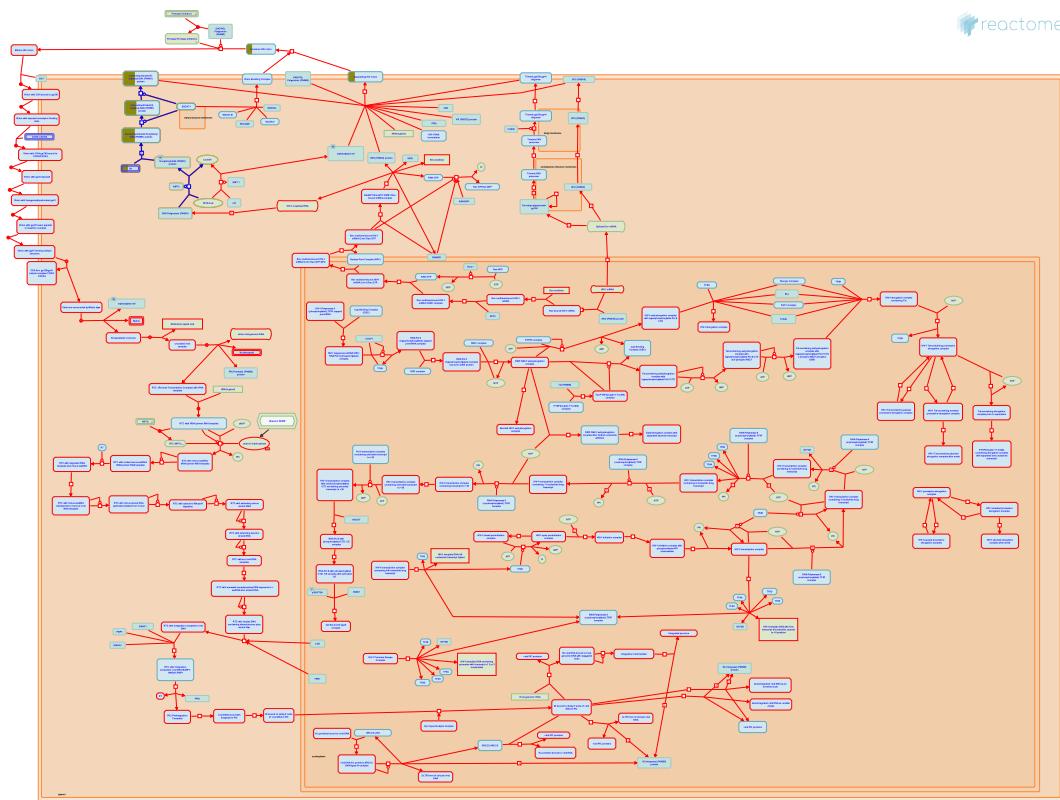
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2020-11-30	Created	Stephan R
2021-01-23	Reviewed	Somers J
2021-11-26	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

Input	UniProt Id
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## 17. Membrane binding and targetting of GAG proteins (R-HSA-174490)



**Diseases:** Human immunodeficiency virus infectious disease.

One of the mysteries of Gag protein involvement in HIV virion assembly is how the proteins are targeted to the proper membrane for budding. Infectious retroviruses do not bud from all of the available membrane surfaces within an infected cell, but primarily from the plasma membrane, which constitutes a small proportion of the total membrane surface in most cells. In polarized cells, the sites of budding are further restricted to the basolateral membrane.

### References

Resh MD & Perlman M (2006). Identification of an intracellular trafficking and assembly pathway for HIV-1 gag. *Traffic*, 7, 731-45. [\[link\]](#)

Sundquist WI & Morita E (2004). Retrovirus budding. *Annu Rev Cell Dev Biol*, 20, 395-425. [\[link\]](#)

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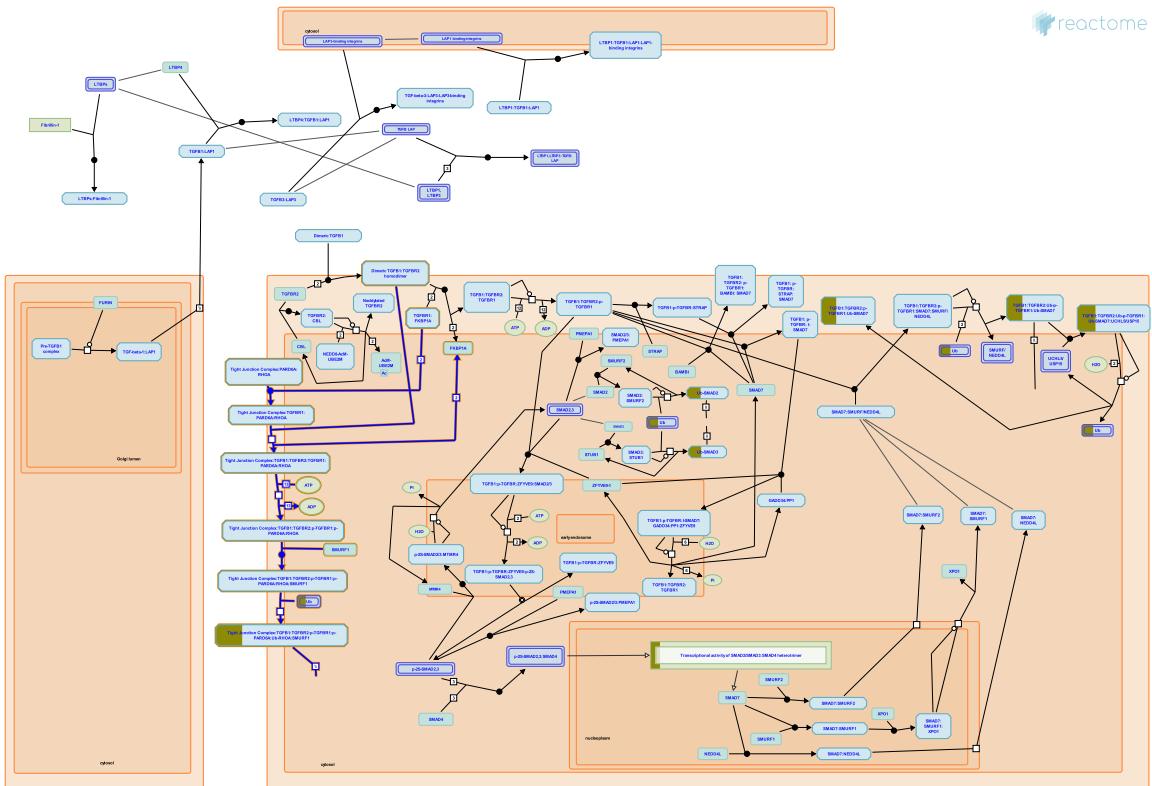
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2013-03-07	Authored	Gillespie ME
2013-05-21	Reviewed	Dube M
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987



18. TGF-beta receptor signaling in EMT (epithelial to mesenchymal transition) ([R-HSA-2173791](#))



In normal cells and in the early stages of cancer development, signaling by TGF-beta plays a tumor suppressive role, as SMAD2/3:SMAD4-mediated transcription inhibits cell division by downregulating MYC oncogene transcription and stimulating transcription of CDKN2B tumor suppressor gene. In advanced cancers however, TGF-beta signaling promotes metastasis by stimulating epithelial to mesenchymal transition (EMT).

TGFBR1 is recruited to tight junctions by binding PARD6A, a component of tight junctions. After TGF-beta stimulation, activated TGFBR2 binds TGFBR1 at tight junctions, and phosphorylates both TGFBR1 and PARD6A. Phosphorylated PARD6A recruits SMURF1 to tight junctions. SMURF1 is able to ubiquitinate RHOA, a component of tight junctions needed for tight junction maintenance, leading to disassembly of tight junctions, an important step in EMT (Wang et al. 2003, Ozdamar et al. 2005).

## References

- Barrios-Rodiles M, Zhang Y, Wrana JL, Wang HR, Bose R & Ozdamar B (2005). Regulation of the polarity protein Par6 by TGF $\beta$  receptors controls epithelial cell plasticity. *Science*, 307, 1603-9. 

Zhang Y, Thomsen GH, Wrana JL, Wang HR, Ogunjimi AA, Ozdamar B & Alexandrova E (2003). Regulation of cell polarity and protrusion formation by targeting RhoA for degradation. *Science*, 302, 1775-9. 

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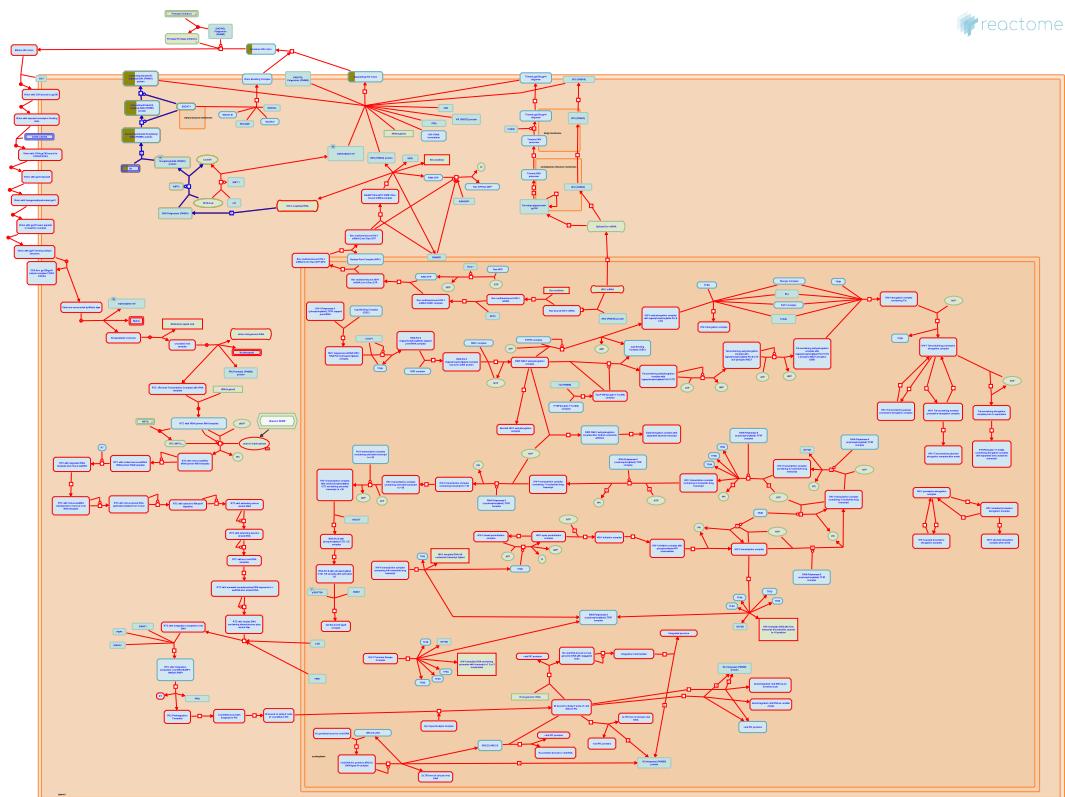
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2012-04-10	Edited	Jassal B
2012-05-14	Reviewed	Huang T
2012-11-14	Reviewed	Chen YG
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 19. Synthesis And Processing Of GAG, GAGPOL Polyproteins (R-HSA-174495)



**Diseases:** Human immunodeficiency virus infectious disease.

Evidence suggests that the RNA molecules used for the synthesis of Gag and Gag-Pro-Pol are not the same molecules that are packaged into virions. Gag proteins do not appear to aggregate around and capture the RNA contained in the polyribosome from which they emerged, but rather bind to and ultimately encapsidate free transcripts elsewhere. During the replication of retroviruses, large numbers of Gag molecules must be generated to serve as precursors to the structural proteins of the virions. Retroviruses have developed a mechanism that permits expression of the Gag protein at high levels relative to the protein sequences encoded in the pro and pol genes, while retaining coregulated expression. This linkage results from the use of the same initiation codon in the same mRNA to express the gag, pro, and pol genes. Translation of this RNA leads occasionally to synthesis of a fusion protein that is usually called the Gag-Pol precursor but is now more appropriately called the Gag-Pro-Pol precursor

### References

Varmus HE, Hughes SH & Coffin JM (1997). *Synthesis, Assembly, and Processing of Viral Proteins, Retroviruses*.

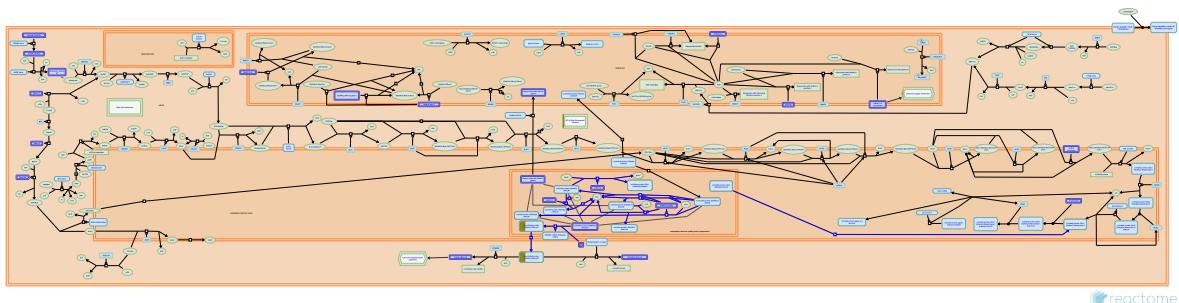
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2013-03-07	Authored	Gillespie ME
2013-05-21	Reviewed	Dube M
2022-01-09	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 20. ER Quality Control Compartment (ERQC) (R-HSA-901032)



Proteins that are released from the CNX or CRT complex with folding defects accumulate in a compartment of the ER called ERQC (Kamhi-Nesher et al. 2001). Here, the enzymes UGGG1 or UGGG2 are able to recognize glycoproteins with minor folding process and re-add the glucose on the alpha,1,3 branch; this is a signal for the transport of these glycoproteins back to the ER, where they can interact again with CNX or CRT in order to achieve a correct folding. At the same time that the glycoprotein is in the ERQC, the enzyme ER mannosidase I progressively removes the mannoses at positions 1A, 2A, B, C on N-glycans; when the mannose on 1A is trimmed, UDP-Glc:glycoprotein glucosyltransferases 1 and 2 (UGGT1 and 2) are no longer able to re-add the glucose, and therefore the protein is destined for ERAD. Glycoproteins subject to endoplasmic reticulum-associated degradation (ERAD) undergo reglucosylation, deglucosylation, and mannose trimming to yield Man6GlcNAc2 and Man5GlcNAc2. These structures lack the mannose residue that is the acceptor of glucose transferred by UGGT1 and 2. For years it has been thought that the removal of the mannose in position B of the N-glycan was the signal to direct proteins to degradation. However, this mechanism has been described better by Avezov et al (Avezov et al. 2008) and it has been demonstrated that even glycoproteins with Man8 or Man7 glycans can be re-glucosylated and interact again with CNX or CRT (for a review on this topic, see Lederkremer 2009 and Maattanen P et al, 2010).

## References

- Lederkremer GZ (2009). Glycoprotein folding, quality control and ER-associated degradation. *Curr Opin Struct Biol*, 19, 515-23. [View](#)
- Thomas DY, Bergeron JJ, Gehring K & Mäkinen P (2010). Protein quality control in the ER: the recognition of misfolded proteins. *Semin Cell Dev Biol*, 21, 500-11. [View](#)
- Herscovics A, Ehrlich M, Lederkremer GZ, Avezov E & Frenkel Z (2008). Endoplasmic reticulum (ER) mannosidase I is compartmentalized and required for N-glycan trimming to Man5-6GlcNAc2 in glycoprotein ER-associated degradation. *Mol Biol Cell*, 19, 216-25. [View](#)
- Fromm SV, Ehrlich R, Lederkremer GZ, Shenkman M, Kamhi-Nesher S & Tolchinsky S (2001). A novel quality control compartment derived from the endoplasmic reticulum. *Mol Biol Cell*, 12, 1711-23. [View](#)

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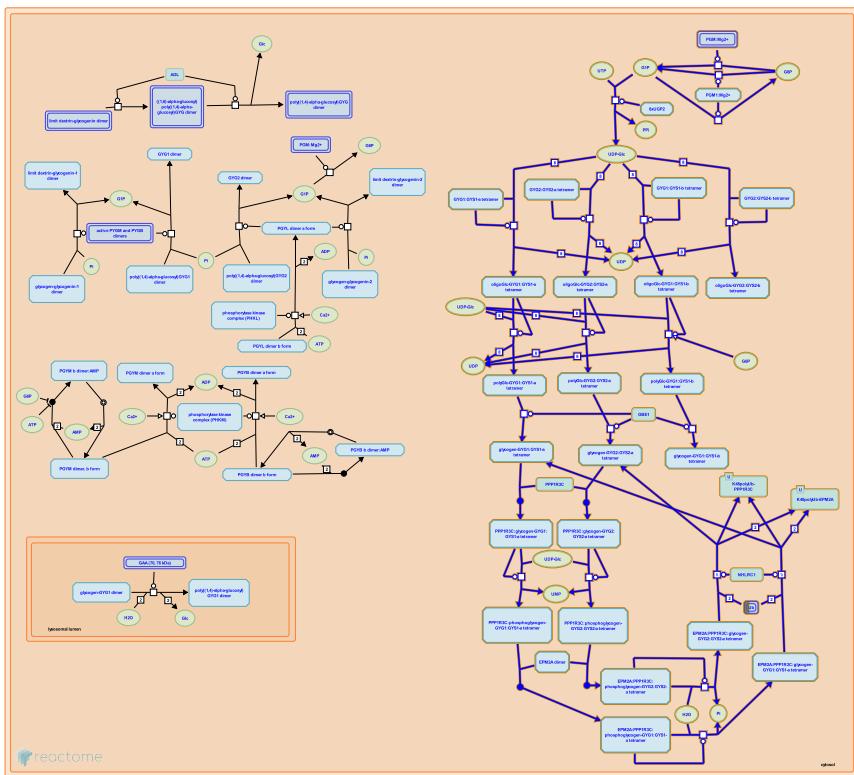
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2010-07-02	Edited	Jassal B
2010-07-02	Created	Jassal B
2010-11-18	Reviewed	Gagneux P

Date	Action	Author
2015-06-03	Revised	Jassal B
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

## 21. Glycogen synthesis (R-HSA-3322077)



Glycogen, a highly branched glucose polymer, is formed and broken down in most human tissues, but is most abundant in liver and muscle, where it serves as a major stored fuel. Glycogen metabolism has been studied in most detail in muscle, although considerable experimental data are available concerning these reactions in liver as well. Glycogen metabolism in other tissues has not been studied as extensively, and is thought to resemble the muscle process. Glycogen synthesis involves five reactions. The first two, conversion of glucose 6-phosphate to glucose 1-phosphate and synthesis of UDP-glucose from glucose 1-phosphate and UTP, are shared with several other pathways. The next three reactions, the auto-catalyzed synthesis of a glucose oligomer on glycogenin, the linear extension of the glucose oligomer catalyzed by glycogen synthase, and the formation of branches catalyzed by glycogen branching enzyme, are unique to glycogen synthesis. Repetition of the last two reactions generates large, extensively branched glycogen polymers. The catalysis of glycogenin glucosylation and oligoglucose chain extension by distinct isozymes in liver and non-hepatic tissues allows them to be regulated independently (Agius 2008; Bollen et al. 1998; Roach et al. 2012).

## References

- Hurley TD, Roach PJ, Tagliabracci VS & DePaoli-Roach AA (2012). Glycogen and its metabolism: some new developments and old themes. *Biochem. J.*, 441, 763-87. [🔗](#)
- Keppens S, Stalmans W & Bollen M (1998). Specific features of glycogen metabolism in the liver. *Biochem. J.*, 336, 19-31. [🔗](#)
- Agius L (2008). Glucokinase and molecular aspects of liver glycogen metabolism. *Biochem. J.*, 414, 1-18. [🔗](#)

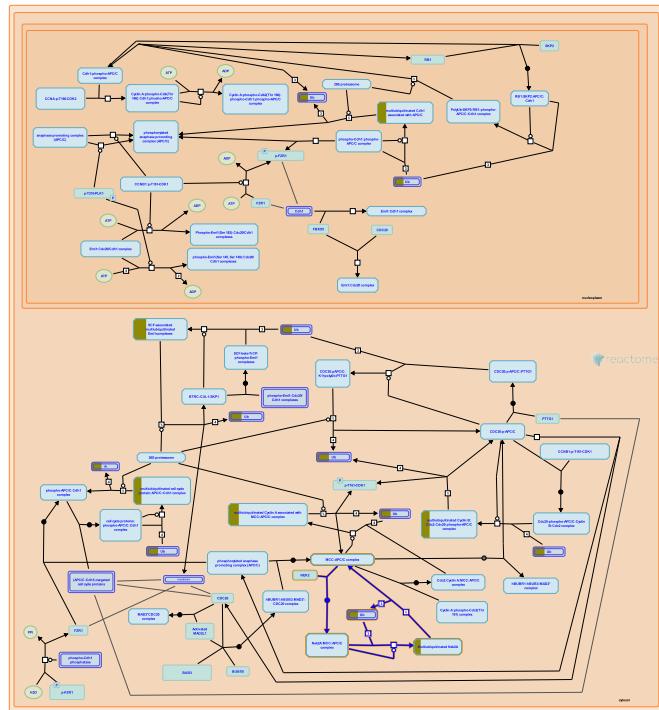
## Edit history

Date	Action	Author
2003-02-15	Authored	
2010-01-22	Revised	D'Eustachio P
2013-05-03	Created	D'Eustachio P
2013-07-26	Reviewed	Jassal B
2013-08-25	Revised	D'Eustachio P
2014-02-19	Revised	D'Eustachio P
2017-03-18	Edited	D'Eustachio P
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

## 22. APC-Cdc20 mediated degradation of Nek2A (R-HSA-179409)



**Cellular compartments:** cytosol.

Like Cyclin A, NIMA-related kinase 2A (Nek2A) is degraded during pro-metaphase in a checkpoint-independent manner.

## References

Fry AM, Bacchieri R, Yamano H, Wattam SL & Hames RS (2001). APC/C-mediated destruction of the centrosomal kinase Nek2A occurs in early mitosis and depends upon a cyclin A-type D-box. EMBO J, 20, 7117-27. [\[PubMed\]](#)

Fry AM, Mao G, Kimata Y, Hayes MJ, Lindon C, Yamano H & Wattam SL (2006). Early mitotic degradation of Nek2A depends on Cdc20-independent interaction with the APC/C. Nat Cell Biol, 8, 607-14. [\[PubMed\]](#)

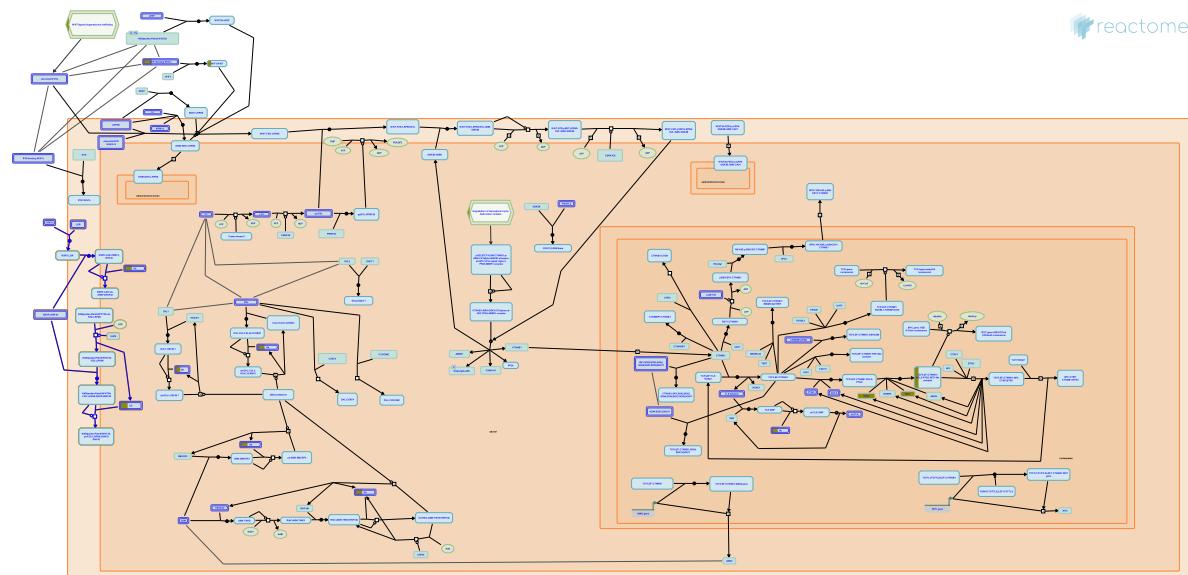
## Edit history

Date	Action	Author
2006-01-26	Authored	Castro A, Lorca T
2006-03-28	Reviewed	Peters JM
2006-04-28	Created	Matthews L
2006-07-11	Edited	Matthews L
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. Regulation of FZD by ubiquitination (R-HSA-4641263)



WNT responsiveness is influenced by expression levels of FZD and LRP proteins. Levels of these receptors at the cell surface are regulated in part by endocytosis, but the mechanisms are not fully elucidated (Garliardi et al, 2008). A number of recent studies have identified a role for ubiquitination in the localization and turnover of WNT receptors at the plasma membrane. ZNRF3 and RNF43 are E3 ligases that have been shown to ubiquitinate FZD proteins and promote their lysosomal degradation, while the deubiquitinating enzyme USP8 promotes recycling of the receptor back to the plasma membrane (Hao et al, 2012; Mukai et al, 2010). This balance of ubiquitination and deubiquitination is in turn regulated by the R-spondin (RSPO) proteins, agonists of WNT signaling which appear to act by downregulating ZNRF3 and RNF43, thus potentiating both canonical and non-canonical pathways (Hao et al, 2012; reviewed in Abo and Clevers, 2012; Fearon and Spence, 2012, Papartriantafyllou, 2012).

## References

- Gagliardi M, Vincent JP & Piddini E (2008). Endocytosis: a positive or a negative influence on Wnt signalling?. *Traffic*, 9, 1-9. [🔗](#)
- Mickanin C, Zhang Y, Bouwmeester T, Zamponi R, Xie Y, Liu D, ... Mao X (2012). ZNRF3 promotes Wnt receptor turnover in an R-spondin-sensitive manner. *Nature*, 485, 195-200. [🔗](#)
- Watanabe W, Goto S, Komada M, Awano W, Yamamoto-Hino M & Mukai A (2010). Balanced ubiquitylation and deubiquitylation of Frizzled regulate cellular responsiveness to Wg/Wnt. *EMBO J.*, 29, 2114-25. [🔗](#)
- Spence JR & Fearon ER (2012). Cancer biology: a new RING to Wnt signaling. *Curr. Biol.*, 22, R849-51. [🔗](#)
- Abo A & Clevers HC (2012). Modulating WNT receptor turnover for tissue repair. *Nat. Biotechnol.*, 30, 835-6. [🔗](#)

## Edit history

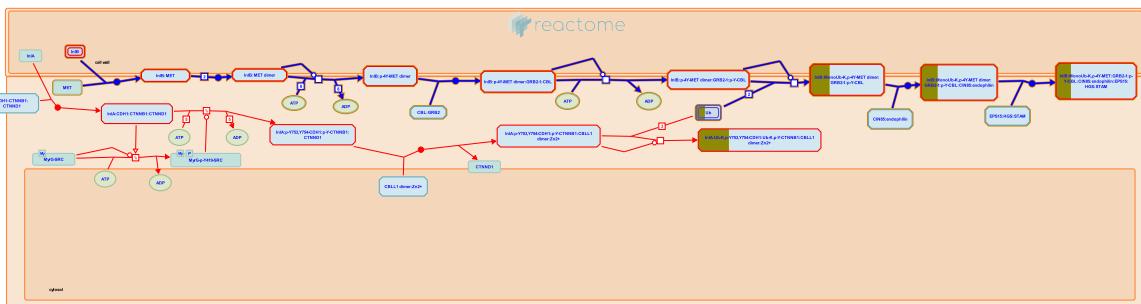
Date	Action	Author
2007-09-04	Edited	Matthews L

Date	Action	Author
2013-09-24	Authored	Rothfels K
2013-09-28	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
2021-11-26	Modified	Weiser JD

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

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## 24. InlB-mediated entry of Listeria monocytogenes into host cell (R-HSA-8875360)



**Diseases:** listeriosis.

InlB, a cell wall protein of *Listeria monocytogenes*, binds MET receptor, acting as an HGF agonist (Shen et al. 2000, Veiga and Cossart 2005). *Listeria monocytogenes* InlB proteins dimerize through their leucine-rich repeat regions (LRRs), promoting dimerization of MET receptors that they are bound to (Ferraris et al. 2010). InlB-induced MET receptor dimerization is followed by MET trans-autophosphorylation and activation of downstream RAS/RAF/MAPK signaling and PI3K/AKT signaling (Niemann et al. 2007, Ferraris et al. 2010). InlB-bound phosphorylated MET receptor recruits the E3 ubiquitin ligase CBL through GRB2. CBL-mediated monoubiquitination of InlB-bound MET promotes endocytosis and entry of *Listeria monocytogenes* to host cells (Veiga and Cossart 2005). CIN85 is necessary for endocytosis-mediated entry of *Listeria monocytogenes* triggered by CBL-mediated monoubiquitination of MET (Veiga and Cossart 2005). Proteins involved in clathrin-mediated endocytosis EPS15 and HGS (Hrs) are both necessary for CBL and MET-mediated entry of *Listeria monocytogenes* into host cells (Veiga and Cossart 2005).

A potential coreceptor role of CD44 in InlB-mediated MET activation is contradictory (Jung et al. 2009, Dortet et al. 2010).

## References

- Heinz DW, Gherardi E, Ferraris DM, Niemann HH & Di Y (2010). Ligand-mediated dimerization of the Met receptor tyrosine kinase by the bacterial invasion protein InlB. *J. Mol. Biol.*, 395, 522-32. [🔗](#)
- Veiga E & Cossart P (2005). Listeria hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. *Nat. Cell Biol.*, 7, 894-900. [🔗](#)
- Park M, Naujokas M, Ireton K & Shen Y (2000). InIB-dependent internalization of *Listeria* is mediated by the Met receptor tyrosine kinase. *Cell*, 103, 501-10. [🔗](#)
- Heinz DW, Ferraris D, Schmidt S, Gherardi E, van den Heuvel J, Jäger V, ... Niemann HH (2007). Structure of the human receptor tyrosine kinase met in complex with the *Listeria* invasion protein InlB. *Cell*, 130, 235-46. [🔗](#)
- Orian-Rousseau V, Tenenbaum T, Schwerk C, Matzke A, Niemann HH & Jung C (2009). Involvement of CD44v6 in InlB-dependent *Listeria* invasion. *Mol. Microbiol.*, 72, 1196-207. [🔗](#)

## Edit history

Date	Action	Author
2016-06-04	Created	Orlic-Milacic M

Date	Action	Author
2016-06-15	Authored	Orlic-Milacic M
2016-10-25	Reviewed	Schwerk C
2016-10-27	Edited	Orlic-Milacic M
2022-01-09	Modified	Weiser JD

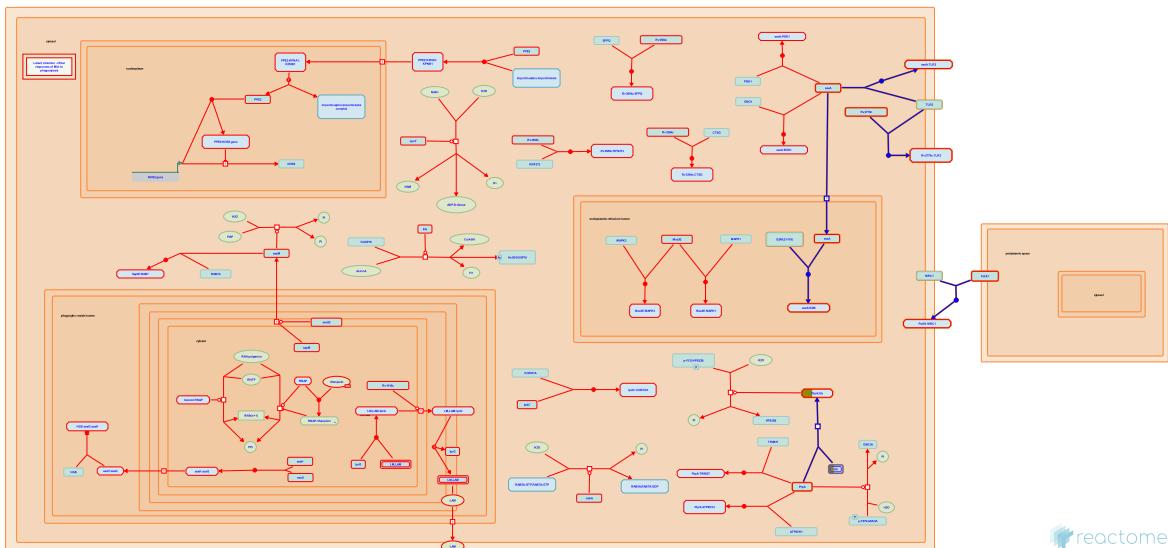
## 1 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id
UBB	P0CG47, P62979, P62987

## Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
PLXNB1	O43157	P08581			

## 25. 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](#)

## Edit history

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

## 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.

### 51 of the submitted entities were found, mapping to 71 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATP13A1	Q9HD20	BRP44	O95563	CACNB2	Q08289
CAPNS1	P04632, Q96L46	CBX6	O95503	CECR1	Q9NZK5
CLPS	P04118	CTRC	Q99895	EPB41L3	Q9Y2J2
FBXW4	P57775	GATM	P50440	GCG	P01275
GNAS	P63092, Q5JWF2	GNB2	P62879	GPC6	Q9Y625
GRIA3	P42263	GSTA1	P08263	GSTA2	P09210
HMGCS1	P54868	KIF5C	O60282	LSAMP	Q13449
LSM7	Q9UK45	MLL2	O14686	MLXIPL	Q9NP71
MZT2B	Q6NZ67	NPC1L1	Q9UHC9-2	PCSK2	P16519
PFDN5	Q99471	PI4KA	P42356	PKD1	P98161
PLXNB1	O43157	PNLIPRP1	P54315, P54317	PRSS1	P07477, P07478
RGNEF	Q8N1W1	RGS2	P41220	RPS4Y1	P22090, Q8TD47
SCARB1	Q8WTW0-2	SCG2	O00255	SMPD1	P17405
SUMF1	Q8NBK3	SYT7	O43581	TCTN1	Q2MV58
TRAPPC2L	Q9UL33	TTR	P02766	TXNIP	Q9H3M7
UBB	P0CG47, P62979, P62987	USH1C	Q9Y6N9	WDR59	Q6PJ19
WEE1	P30291, Q99640	WNT4	O96014, P56705	ZNF331	Q9NQX6

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
GCG	ENSG00000115263	GSTA2	ENSG00000244067	HMGCS1	ENSG00000112972
UBB	ENSG00000170315	WNT4	ENSG00000162552		

### Interactors (42)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
ATP13A1	Q9HD20-3	Q8IWU4	BRP44	O95563	P02654
C15orf48	Q9C002	P42858	C19orf63	Q5UCC4	Q8N4V1
CACNB2	Q08289	O14744	CAPNS1	P04632	P13569
CBFA2T2	O43439-4	Q9BRV8	CBX6	O95503	P11940
EPB41L3	Q9Y2J2	P49841	ERP27	Q96DN0	P29692
FBXW4	P57775	P62308	GATM	P50440	Q13352
GCG	P01275	P01275, P48546	GNAS	P63092	P30988
GNB2	P62879	P61081	KIAA1324	Q6UXG2-3	P14136
LGALS2	P05162	O00560	LSAMP	Q13449	Q13352
LSM7	Q9UK45	P62306, P62318	MLL2	Q9UMN6	O00255
PFDN5	Q99471	Q13163, Q13164	PI4KA	P42356	P19320
PKD1	Q15139	P02795	PLXNB1	O43157	P08581
PNLIPRP1	P54315	Q7Z5P4	PRRC2B	Q5JSZ5	Q96KQ7
RGNEF	Q8N1W1-4	P27797	RGS2	P41220	P11142
SCARB1	Q8WTW0-2	P02649	SCG2	O00255	Q9BXW9
SLIRP	Q9GZT3	P05919	SUMF1	Q8NBK3	Q8NBK3, Q8NBJ7
SYT7	O43581	Q8IUQ4	TRAPPC2L	Q9UL33-2	P50458

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
TTR	O55245, P02766	P02753	TXNIP	Q9H3M7	P10599
UBB	P0CG47	Q9HAU4	UNC119	Q13432	P36404
USH1C	Q9Y6N9-4	P54646	WDR59	Q6PJI9	P55735
WEE1	P30291	Q9Y297	ZNF331	Q9NQX6	O15397

## 7. Identifiers not found

These 16 identifiers were not found neither mapped to any entity in Reactome.

C17orf110	C1orf122	CALY	FEV	GPR64	KIAA1244	NENF	PCP4
RBM33	REG1A	SCG5	SERPINI2	SNX29	SPINK1	TMED6	TRY6