



# 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=MjAyMjAyMjYwMzM1NTFfMTczMDQ%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:

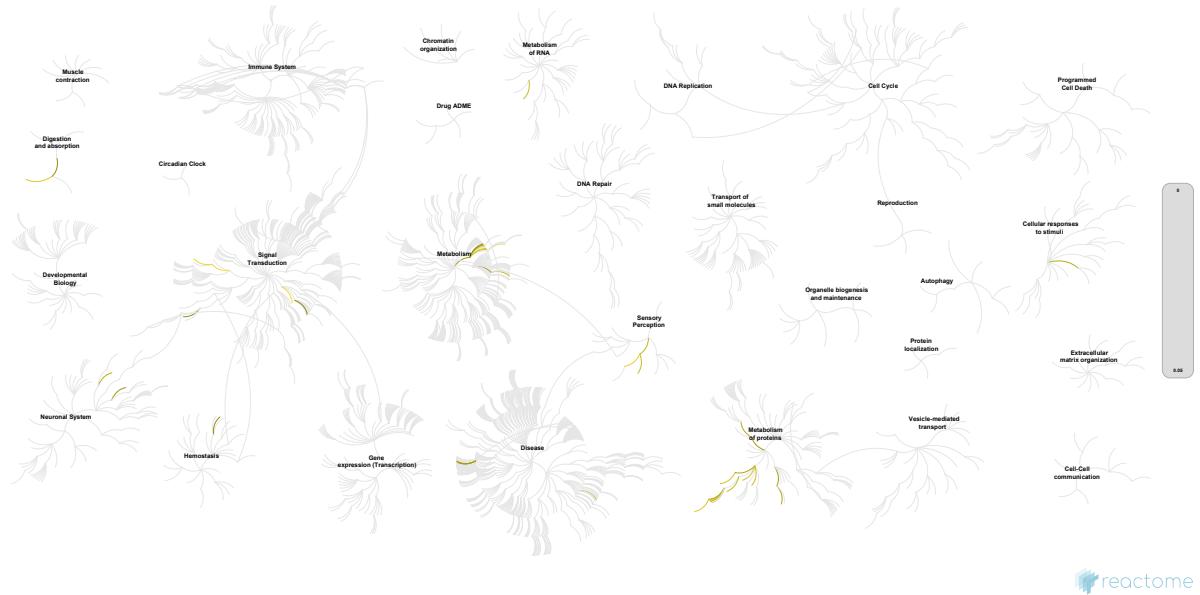
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 23 out of 27 identifiers in the sample were found in Reactome, where 379 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 MjAyMjAyMjYwMzM1NTFfMTczMDQ%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    |
| Class B/2 (Secretin family receptors)  | 4 / 130  | 0.006    | 9.88e-05 | 0.041 | 5 / 20    | 0.001    |
| WNT ligand biogenesis and trafficking  | 2 / 35   | 0.002    | 0.002    | 0.376 | 8 / 12    | 8.79e-04 |
| Glucagon-type ligand receptors   | 2 / 50   | 0.002    | 0.004    | 0.376 | 4 / 8     | 5.86e-04 |
| Formation of the ternary complex, and subsequently, the 43S complex          | 2 / 54   | 0.002    | 0.005    | 0.376 | 1 / 3     | 2.20e-04 |
| Glucagon signaling in metabolic regulation                                   | 2 / 59   | 0.003    | 0.005    | 0.376 | 2 / 6     | 4.40e-04 |
| Glucagon-like Peptide-1 (GLP1) regulates insulin secretion                   | 2 / 69   | 0.003    | 0.007    | 0.376 | 3 / 11    | 8.06e-04 |
| Ribosomal scanning and start codon recognition                               | 2 / 70   | 0.003    | 0.007    | 0.376 | 2 / 2     | 1.47e-04 |
| Sensory processing of sound by outer hair cells of the cochlea               | 2 / 73   | 0.003    | 0.008    | 0.376 | 1 / 8     | 5.86e-04 |
| Intestinal lipid absorption  | 1 / 6    | 2.69e-04 | 0.011    | 0.376 | 3 / 3     | 2.20e-04 |
| PKA-mediated phosphorylation of key metabolic factors                        | 1 / 7    | 3.14e-04 | 0.013    | 0.376 | 4 / 5     | 3.66e-04 |
| Translation initiation complex formation                                     | 3 / 97   | 0.004    | 0.014    | 0.376 | 2 / 2     | 1.47e-04 |
| Peptide chain elongation   | 2 / 103  | 0.005    | 0.016    | 0.376 | 4 / 5     | 3.66e-04 |
| PP2A-mediated dephosphorylation of key metabolic factors                     | 1 / 9    | 4.04e-04 | 0.016    | 0.376 | 3 / 4     | 2.93e-04 |
| Eukaryotic Translation Termination   | 2 / 109  | 0.005    | 0.017    | 0.376 | 3 / 5     | 3.66e-04 |
| Formation of a pool of free 40S subunits                                     | 2 / 111  | 0.005    | 0.018    | 0.376 | 2 / 2     | 1.47e-04 |
| Selenocysteine synthesis   | 2 / 115  | 0.005    | 0.019    | 0.376 | 2 / 7     | 5.13e-04 |
| SRP-dependent cotranslational protein targeting to membrane                  | 2 / 119  | 0.005    | 0.02     | 0.376 | 5 / 5     | 3.66e-04 |
| Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex (EJC) | 2 / 121  | 0.005    | 0.021    | 0.376 | 1 / 1     | 7.33e-05 |
| Sensory processing of sound by inner hair cells of the cochlea               | 2 / 123  | 0.006    | 0.022    | 0.376 | 1 / 7     | 5.13e-04 |
| L13a-mediated translational silencing of Ceruloplasmin expression            | 2 / 124  | 0.006    | 0.022    | 0.376 | 1 / 3     | 2.20e-04 |
| Sensory processing of sound  | 2 / 134  | 0.006    | 0.025    | 0.376 | 2 / 13    | 9.53e-04 |
| Viral mRNA Translation   | 2 / 135  | 0.006    | 0.026    | 0.376 | 2 / 2     | 1.47e-04 |

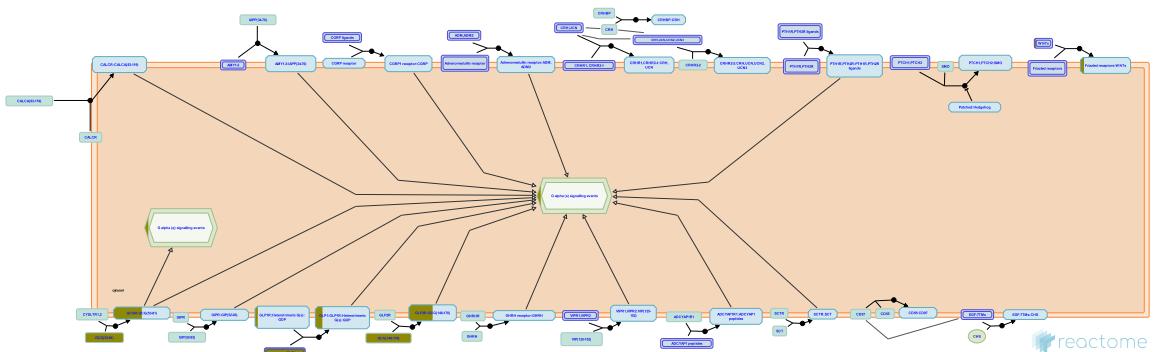
| Pathway name   | Entities |          |         |       | Reactions |          |
|--|----------|----------|---------|-------|-----------|----------|
|  | found    | ratio    | p-value | FDR*  | found     | ratio    |
| Activation of AMPA receptors                         | 1 / 16   | 7.18e-04 | 0.029   | 0.376 | 5 / 5     | 3.66e-04 |
| Defective EXT1 causes exostoses 1,<br>TRPS2 and CHDS | 1 / 16   | 7.18e-04 | 0.029   | 0.376 | 4 / 4     | 2.93e-04 |
| Defective EXT2 causes exostoses 2                    | 1 / 16   | 7.18e-04 | 0.029   | 0.376 | 4 / 4     | 2.93e-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. 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. [View](#)

### 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     |

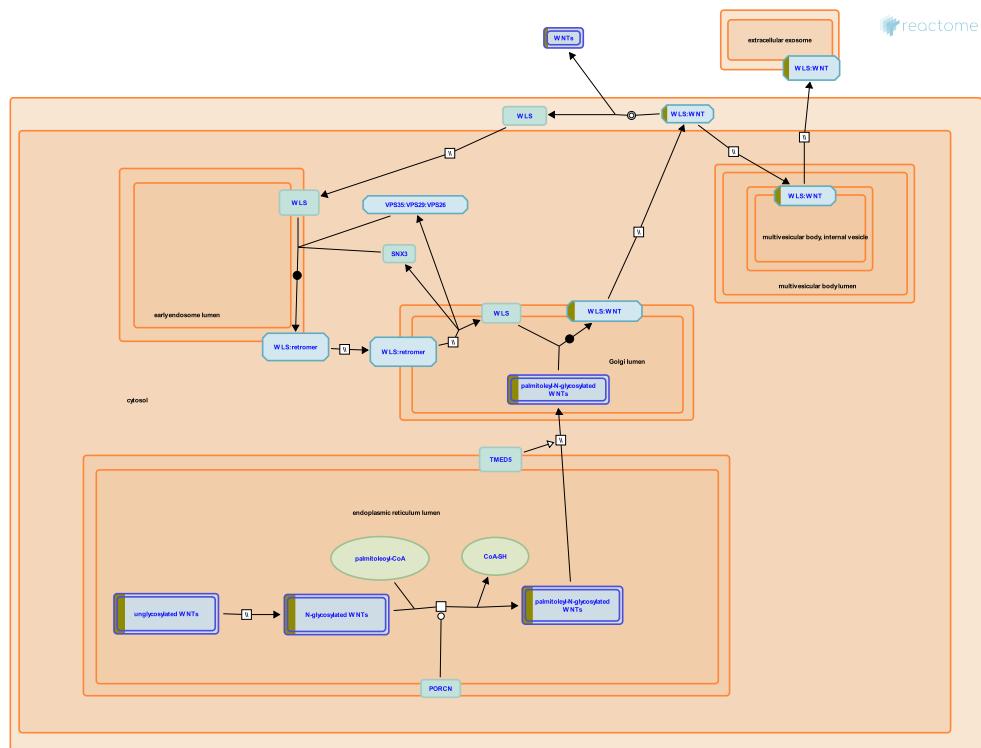
### 3 submitted entities found in this pathway, mapping to 4 Reactome entities

| Input | UniProt Id | Input | UniProt Id | Input | UniProt Id     |
|-------|------------|-------|------------|-------|----------------|
| GCG   | P01275     | GNB2  | P62879     | WNT4  | O96014, P56705 |

### Interactors found in this pathway (1)

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

## 2. WNT ligand biogenesis and trafficking (R-HSA-3238698)



19 WNT proteins have been identified in human cells. The WNTs are members of a conserved metazoan family of secreted morphogens that activate several signaling pathways in the responding cell: the canonical (beta-catenin) WNT signaling cascade and several non-canonical pathways, including the planar cell polarity (PCP), the regulation of intracellular calcium signaling and activation of JNK kinases. WNT proteins exist in a gradient outside the secreting cell and are able to act over both short and long ranges to promote proliferation, changes in cell migration and polarity and tissue homeostasis, among others (reviewed in Saito-Diaz et al, 2012; Willert and Nusse, 2012).

The WNTs are ~40kDa proteins with 23 conserved cysteine residues in the N-terminal that may form intramolecular disulphide bonds. They also contain an N-terminal signal sequence and a number of N-linked glycosylation sites (Janda et al, 2012). In addition to being glycosylated, WNTs are also lipid-modified in the endoplasmic reticulum by a WNT-specific O-acyl-transferase, Porcupine (PORCN), contributing to their characteristic hydrophobicity. PORCN-dependent palmitoylation is required for the secretion of WNT as well as its signaling activity, as either depletion of PORCN or mutation of the conserved serine acylation site results in the intracellular accumulation of WNT ligand (Takada et al, 2006; Barrott et al, 2011; Biechele et al, 2011; reviewed in Willert and Nusse, 2012).

Secretion of WNT requires a number of other dedicated factors including the sorting receptor Wntless (WLS) (also known as Evi, Sprinter, and GPR177), which binds WNT and escorts it to the cell surface (Banziger et al, 2006; Bartscherer et al, 2006; Goodman et al, 2006). A WNT-specific retromer containing SNX3 is subsequently required for the recycling of WLS back to the Golgi (reviewed in Herr et al, 2012; Johannes and Wunder, 2011). Once at the cell surface, WNT makes extensive contacts with components of the extracellular matrix such as heparan sulphate proteoglycans (HSPGs) and may be bound by any of a number of regulatory proteins, including WIFs and SFRPs. The diffusion of the WNT ligand may be aided by its packing either into WNT multimers, exosomes or onto lipoprotein particles to shield the hydrophobic lipid adducts from the aqueous extracellular environment (Gross et al, 2012; Luga et al, 2012, Korkut et al, 2009; reviewed in Willert and Nusse, 2012).

<br>

## References

- Zipperlen P, Soldini D, Banziger C, Hausmann G, Schätt C & Basler K (2006). Wntless, a conserved membrane protein dedicated to the secretion of Wnt proteins from signaling cells. *Cell*, 125, 509-22. [\[View\]](#)
- Barrow JR, Barrott JJ, Murtaugh LC, Smith AP & Cash GM (2011). Deletion of mouse Porcn blocks Wnt ligand secretion and reveals an ectodermal etiology of human focal dermal hypoplasia/Goltz syndrome. *Proc. Natl. Acad. Sci. U.S.A.*, 108, 12752-7. [\[View\]](#)
- Herr P, Hausmann G & Basler K (2012). WNT secretion and signalling in human disease. *Trends Mol Med*, 18, 483-93. [\[View\]](#)
- Nusse R & Willert K (2012). Wnt proteins. *Cold Spring Harb Perspect Biol*, 4, a007864. [\[View\]](#)
- Bartscherer K, Boutros M, Pelte N & Ingelfinger D (2006). Secretion of Wnt ligands requires Evi, a conserved transmembrane protein. *Cell*, 125, 523-33. [\[View\]](#)

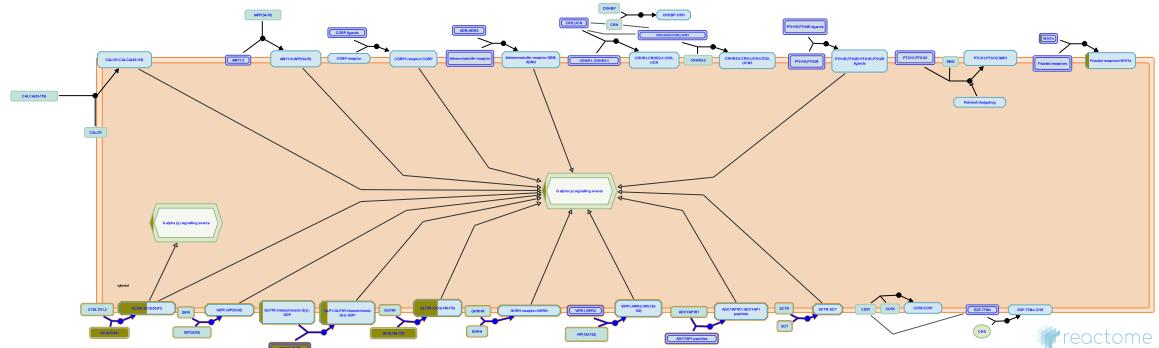
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| 2013-03-27 | Created  | Rothfels K |
| 2013-04-06 | Authored | Rothfels K |
| 2013-04-12 | Edited   | Matthews L |
| 2013-05-24 | Reviewed | Boutros M  |
| 2021-11-28 | Modified | Weiser JD  |

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

| Input | UniProt Id     |
|-------|----------------|
| WNT4  | O96014, P56705 |

### 3. 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

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| 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     |

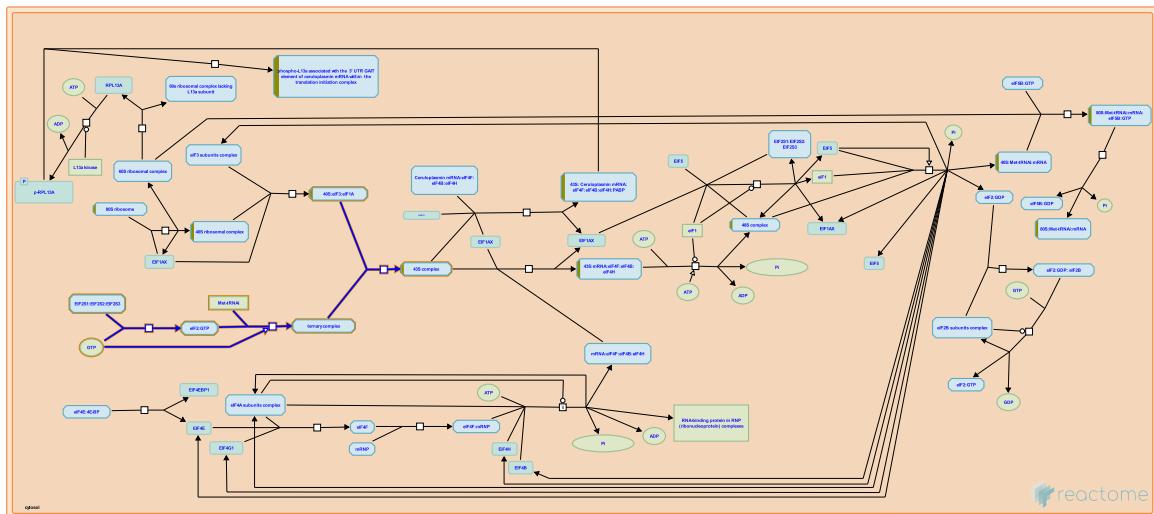
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| GCG   | P01275     | GNB2  | P62879     |

## Interactors found in this pathway (1)

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

#### 4. Formation of the ternary complex, and subsequently, the 43S complex (R-HSA-72695)



**Cellular compartments:** cytosol.

Binding of the methionyl-tRNA initiator to the active eIF2:GTP complex results in the formation of the ternary complex. Subsequently, this Met-tRNAi:eIF2:GTP (ternary) complex binds to the complex formed by the 40S subunit, eIF3 and eIF1A, to form the 43S complex.

#### References

- Erni B, Schreier MH, Trachsel H & Staehelin T (1978). Initiation of mammalian protein synthesis. II. The assembly of the initiation complex with purified initiation factors. *J Mol Biol*, 116, 755-67. [🔗](#)
- Benne R & Hershey JW (1978). The mechanism of action of protein synthesis initiation factors from rabbit reticulocytes. *J Biol Chem*, 253, 3078-87. [🔗](#)
- Anderson WF, Safer B, Adams SL & Merrick WC (1976). Binding of MET-TRNAf and GTP to homogeneous initiation factor MP. *J Biol Chem*, 250, 9076-82. [🔗](#)
- McCarthy JE & Tuite M (1990). *New insights into an old problem: ternary complex (Met-tRNAf.eIF.GTP) formation in animal cells., Post-Transcriptional Control of Gene Expression*, 521-526.
- Safer B, Peterson DT & Merrick WC (1979). Binding and release of radiolabeled eukaryotic initiation factors 2 and 3 during 80 S initiation complex formation. *J Biol Chem*, 254, 2509-16. [🔗](#)

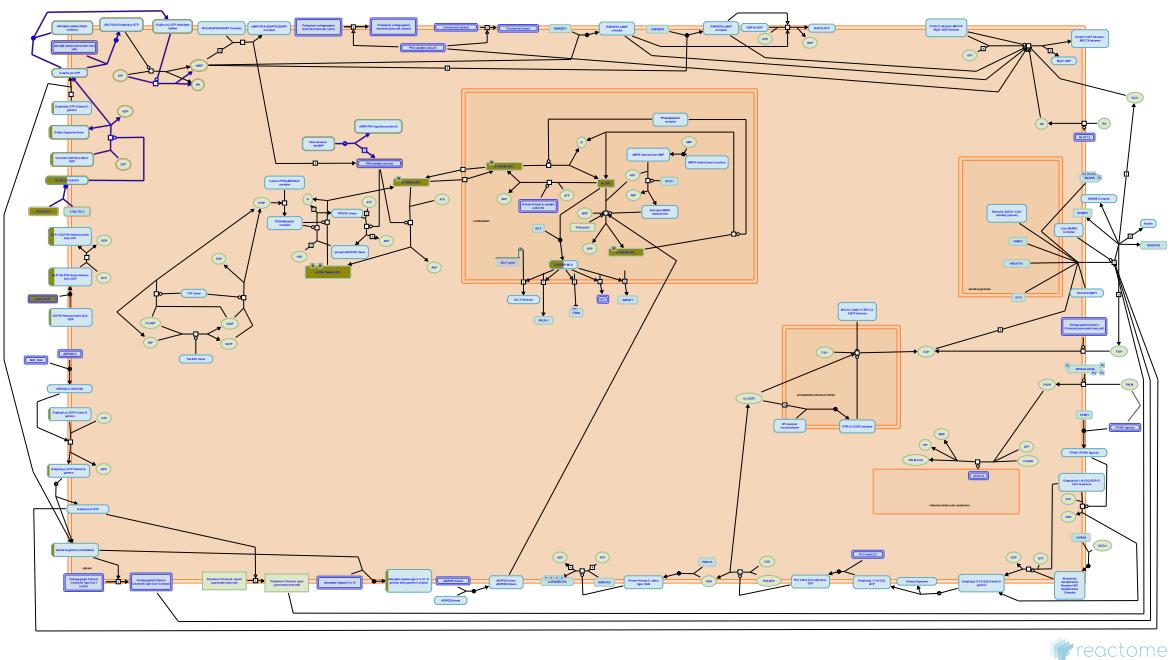
#### Edit history

| Date       | Action   | Author    |
|------------|----------|-----------|
| 2021-11-28 | Modified | Weiser JD |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

## 5. 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.

### Edit history

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

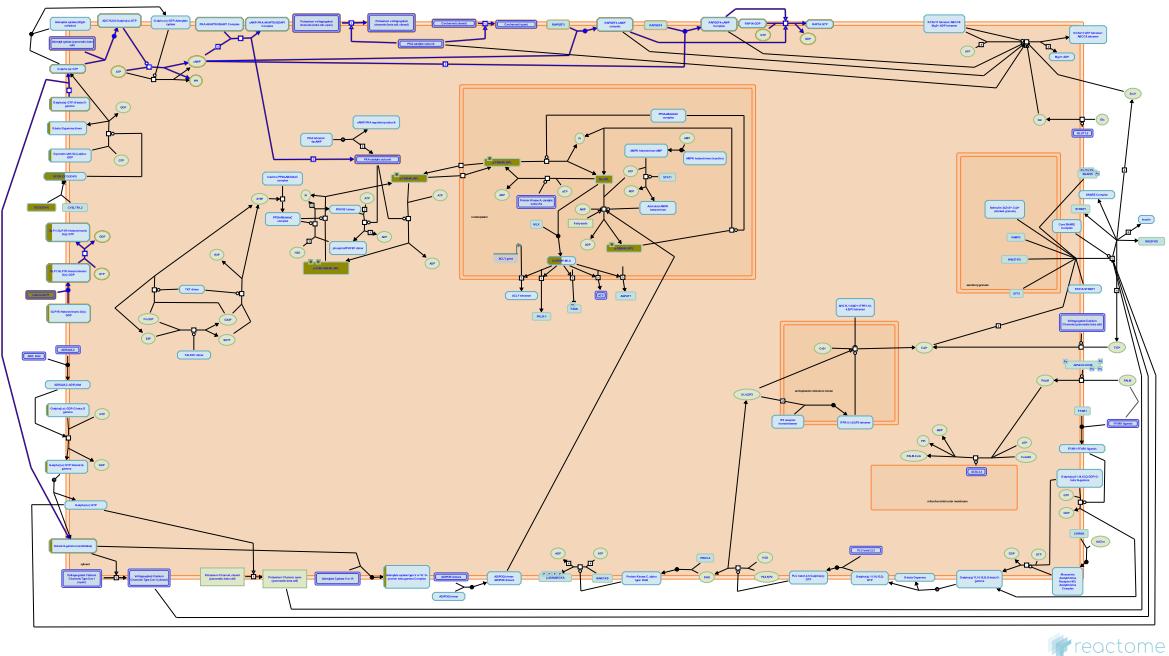
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| GCG   | P01275     | GNB2  | P62879     |

### Interactors found in this pathway (1)

| Input | UniProt Id | Interacts with | Input | UniProt Id | Interacts with |
|-------|------------|----------------|-------|------------|----------------|
| GCG   | P01275     | P01275         |       |            |                |

## 6. 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. [🔗](#)

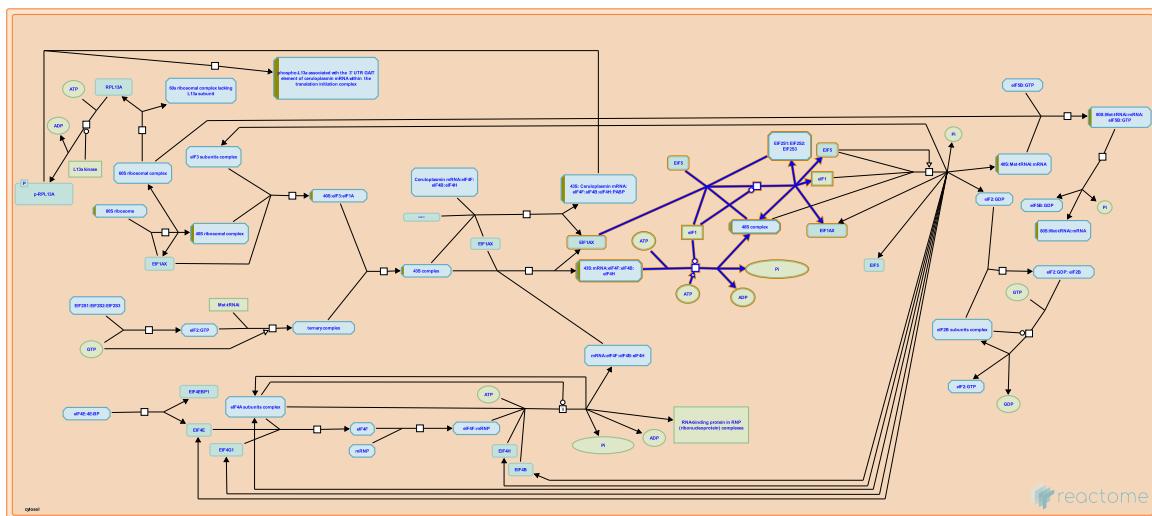
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| 2009-05-28 | Authored | May B        |
| 2009-06-02 | Reviewed | Gillespie ME |
| 2021-11-28 | Modified | Weiser JD    |

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

| Input | UniProt Id | Input | UniProt Id |
|-------|------------|-------|------------|
| GCG   | P01275     | GNB2  | P62879     |

## 7. Ribosomal scanning and start codon recognition (R-HSA-72702)



The 80S ribosome bound to the mRNA moves along the mRNA molecule from its initial site to the initiation codon and forms a 48S complex, in which the initiation codon is base paired to the anti-codon of the Met-tRNA<sub>i</sub>. Proper recognition of the AUG initiation codon depends on base pairing with the anticodon of the Met-tRNA<sub>i</sub> and requires eIF1, eIF1A, eIF2 and eIF5.

## References

- Erni B, Schreier MH, Trachsel H & Staehelin T (1978). Initiation of mammalian protein synthesis. II. The assembly of the initiation complex with purified initiation factors. *J Mol Biol*, 116, 755-67. [🔗](#)
- Benne R & Hershey JW (1978). The mechanism of action of protein synthesis initiation factors from rabbit reticulocytes. *J Biol Chem*, 253, 3078-87. [🔗](#)
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- Kozak M (1981). Evaluation of the "scanning model" for initiation of protein synthesis in eucaryotes. *Cell*, 22, 7-8. [🔗](#)
- Hellen CU, Pestova TV & Borukhov SI (1999). Eukaryotic ribosomes require initiation factors 1 and 1A to locate initiation codons. *Nature*, 394, 854-9. [🔗](#)

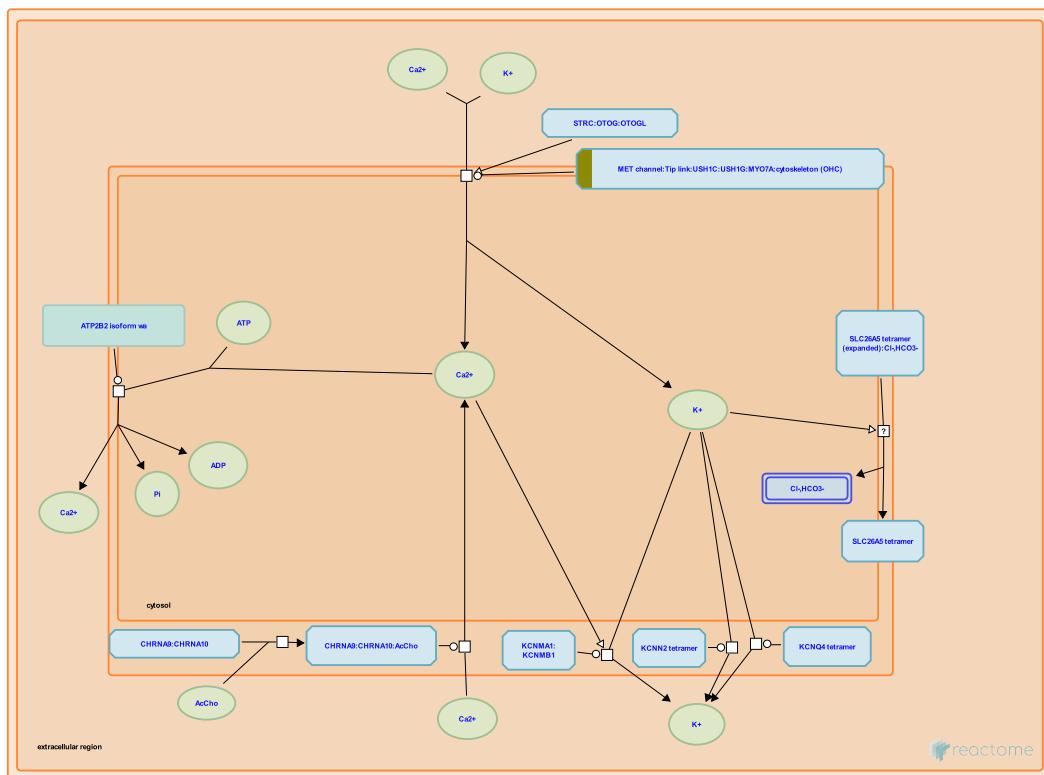
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| 2002-12-16 | Created  | Merrick WC |
| 2021-11-28 | Modified | Weiser JD  |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

## 8. Sensory processing of sound by outer hair cells of the cochlea (R-HSA-9662361 )



Outer hair cells (OHCs) produce amplification of sound waves in the cochlea by shortening and lengthening in response to sound, a phenomenon called electromotility (reviewed in Kim and Fettiplace 2014, Fettiplace 2016, Fettiplace 2017, Fritzsch et al. 2017, Ashmore 2019). Like inner hair cells, OHCs possess apical stereocilia arranged in rows of ascending height. A taller stereocilium is connected to a shorter stereocilium by a tip link comprising a CDH23 dimer on the side of the taller stereocilium and a PCDH15 dimer on the apex of the shorter stereocilium. PCDH15 interacts with LHFPL5, a subunit of the mechanoelectrical transduction channel complex (MET channel, also called the mechanotransduction channel), which contains TMC1 or TMC2, TMIE, CIB2, and LHFPL5 (reviewed in Fettiplace 2016). Deflection of the stereocilia in one direction produces tension on the tip link that increases the open probability of the MET channel, resulting in depolarization of the OHC. Deflection of the stereocilia in the opposite direction produces compression on the tip link that decreases the open probability of the MET channel, resulting in hyperpolarization of the OHC.

Sound causes micromechanical motions of the organ of Corti that result in alternating tension and compression in the tip link that produce excitatory-inhibitory cycles of MET channel openings and closings relative to the MET channel's resting open probability. This causes directionally alternating fluxes of  $\text{K}^+$  and  $\text{Ca}^{2+}$ , yielding depolarization-hyperpolarization cycles that cause conformational changes in prestin (SLC26A5). These cycles are asymmetrical, with contraction caused by depolarization dominating elongation caused by hyperpolarization due to the asymmetry of the open probability of MET channels. Stereociliary ATP2B2 (PMCA2) extrudes calcium ions and basally located KCNQ4 extrudes potassium ions to repolarize the OHC.

Depolarization of the OHC causes a decrease in length of the OHC due to a very rapid, voltage-sensitive change in conformation of the membrane protein prestin (SLC26A5), an unusual member of the anion transporter family located in the lateral membrane (Mahendrasingam et al, 2010) that appears to respond to cytosolic chloride by altering its conformation in the plane of the plasma membrane (reviewed in Dallos et al. 2006, Dallos 2008, Hudspeth 2014, Reichenbach and Hudspeth 2014, Ashmore 2019, Santos-Sacchi 2019). Prestin also appears to act as a weak chloride-bicarbonate antiporter (Mistrik et al. 2012). Changes in length of the OHCs cause movement of the reticular lamina toward and away from the basilar membrane.

## References

- Santos-Sacchi J (2019). The speed limit of outer hair cell electromechanical activity. *HNO*, 67, 159-164. [🔗](#)
- Fritzsch B & Elliott KL (2017). Evolution and Development of the Inner Ear Efferent System: Transforming a Motor Neuron Population to Connect to the Most Unusual Motor Protein via Ancient Nicotinic Receptors. *Front Cell Neurosci*, 11, 114. [🔗](#)
- Fettiplace R (2016). Is TMC1 the Hair Cell Mechanotransducer Channel?. *Biophys. J.*, 111, 3-9. [🔗](#)
- Ashmore JF, Mistrák P, Morandell K & Daudet N (2012). Mammalian prestin is a weak Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> electrogenic antiporter. *J. Physiol. (Lond.)*, 590, 5597-610. [🔗](#)
- Kim KX & Fettiplace R (2014). The physiology of mechanoelectrical transduction channels in hearing. *Physiol. Rev.*, 94, 951-86. [🔗](#)

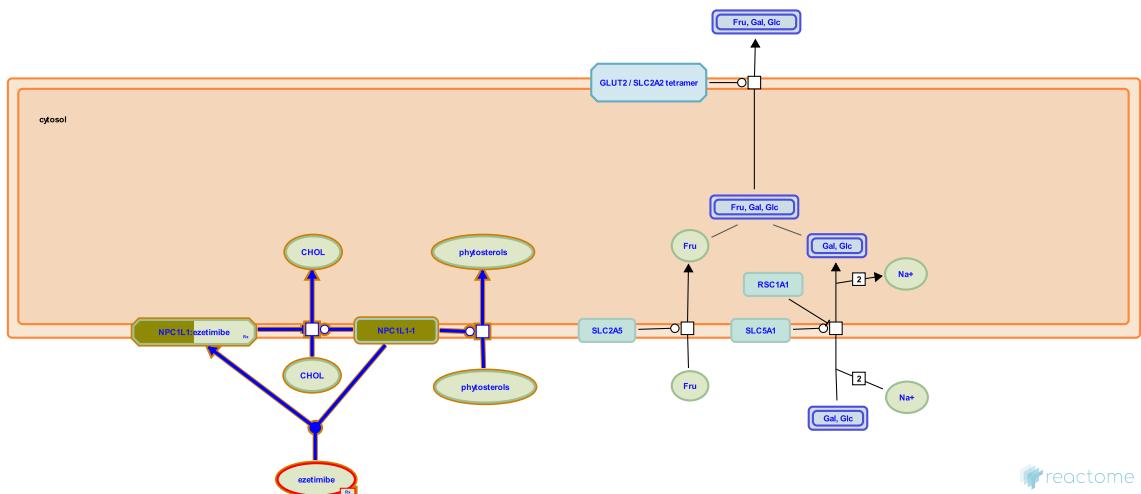
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| 2019-09-23 | Edited   | May B                |
| 2019-09-23 | Authored | May B                |
| 2019-09-23 | Created  | May B                |
| 2020-09-14 | Reviewed | Furness DN, Dallos P |
| 2020-12-12 | Modified | May B                |

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

| Input   | UniProt Id | Input | UniProt Id |
|---------|------------|-------|------------|
| EPB41L3 | Q9Y2J2     | USH1C | Q9Y6N9     |

## 9. Intestinal lipid absorption (R-HSA-8963678)



reactome

Niemann-Pick C1 Like 1 (NPC1L1) protein in enterocytes is critical for intestinal cholesterol and phytosterol absorption, and is the target of the drug ezetimibe (Davis et al. 2004).

## References

Iyer SP, Altmann SW, Detmers PA, Lam MH, Maguire M, Yao X, ... Zhu LJ (2004). Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal phytosterol and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. *J. Biol. Chem.*, 279, 33586-92. [View](#)

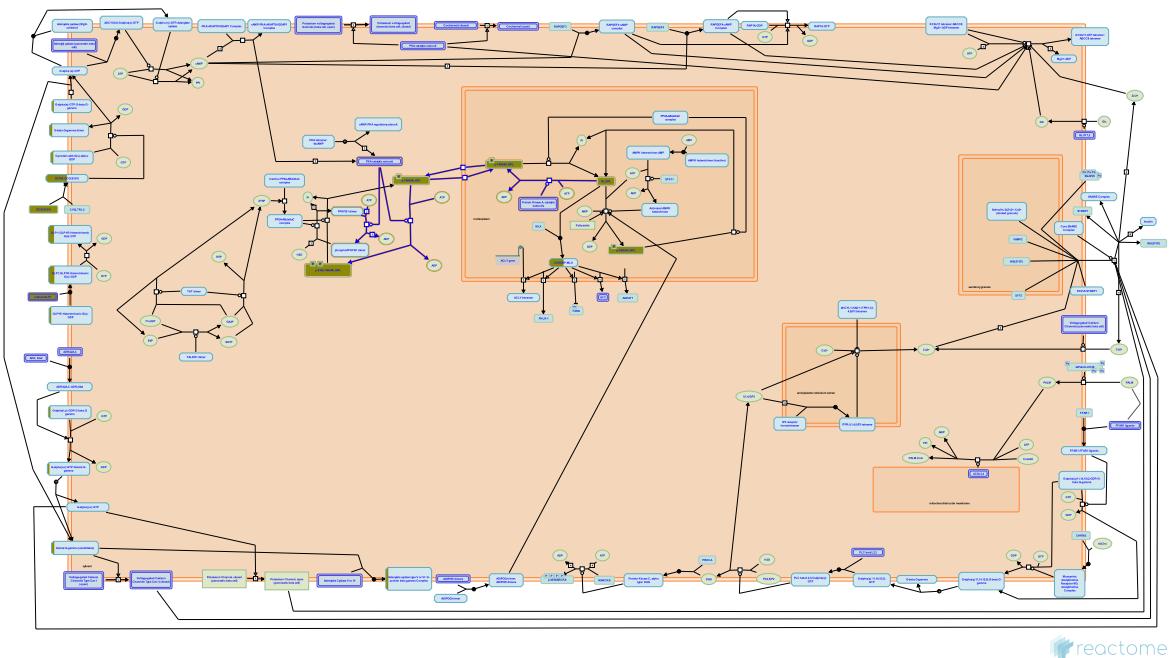
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| 2008-05-12 | Authored | D'Eustachio P |
| 2008-06-13 | Reviewed | Jassal B      |
| 2017-02-10 | Edited   | D'Eustachio P |
| 2017-02-10 | Created  | D'Eustachio P |
| 2021-11-28 | Modified | Weiser JD     |

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

| Input  | UniProt Id |
|--------|------------|
| NPC1L1 | Q9UHC9-2   |

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



**Cellular compartments:** nucleoplasm, cytosol.

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

### References

Veech RL (2003). A humble hexose monophosphate pathway metabolite regulates short- and long-term control of lipogenesis. Proc Natl Acad Sci U S A, 100, 5578-80. [View](#)

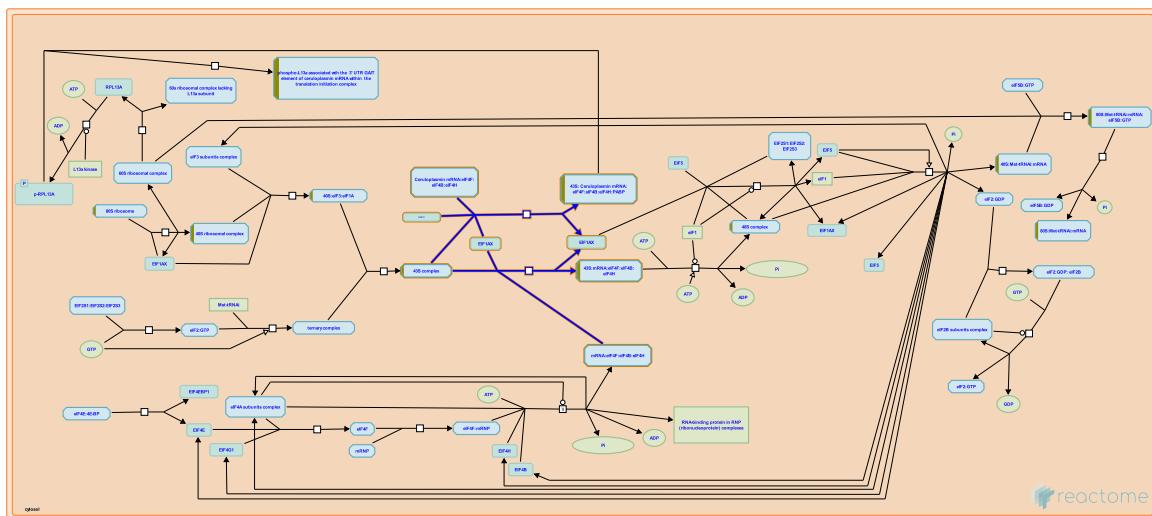
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| 2005-04-28 | Created  | Gopinathrao G |
| 2005-05-13 | Authored | Gopinathrao G |
| 2021-11-27 | Modified | Weiser JD     |

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

| Input  | UniProt Id |
|--------|------------|
| MLXIPL | Q9NP71     |

## 11. Translation initiation complex formation (R-HSA-72649)



**Cellular compartments:** cytosol.

The translation initiation complex forms when the 43S complex binds the mRNA that is associated with eIF4F, eIF4B and eIF4H. eIF4G in the eIF4F complex can directly contact eIF3 in the 43S complex. eIF1A is necessary for the formation of this complex.

### References

Tahara SM, Morgan MA, Grifo JA, Merrick WC & Shatkin AJ (1983). New initiation factor activity required for globin mRNA translation. *J Biol Chem*, 258, 5804-10. [🔗](#)

Erni B, Schreier MH, Trachsel H & Staehelin T (1978). Initiation of mammalian protein synthesis. II. The assembly of the initiation complex with purified initiation factors. *J Mol Biol*, 116, 755-67. [🔗](#)

Benne R & Hershey JW (1978). The mechanism of action of protein synthesis initiation factors from rabbit reticulocytes. *J Biol Chem*, 253, 3078-87. [🔗](#)

Hellen CU, Pestova TV & Borukhov SI (1999). Eukaryotic ribosomes require initiation factors 1 and 1A to locate initiation codons. *Nature*, 394, 854-9. [🔗](#)

### Edit history

| Date       | Action   | Author     |
|------------|----------|------------|
| 2002-12-16 | Created  | Merrick WC |
| 2021-11-27 | Modified | Weiser JD  |

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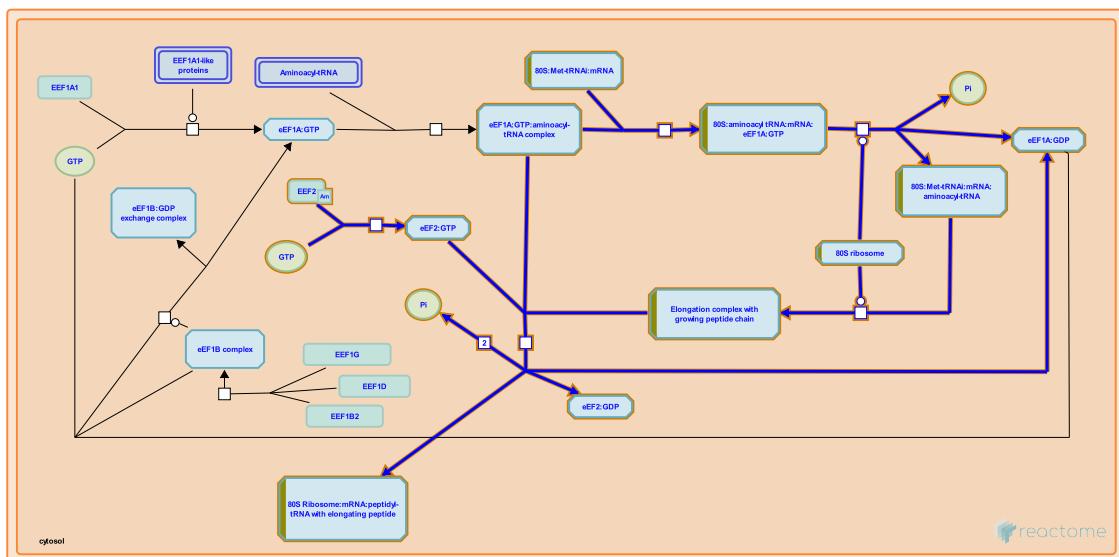
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| RPS4Y1 | P22090, Q8TD47 |

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| CBX6  | O95503     | P11940         |       |            |                |

| Input | UniProt Id | Interacts with | Input | UniProt Id | Interacts with |
|-------|------------|----------------|-------|------------|----------------|
|-------|------------|----------------|-------|------------|----------------|

## 12. Peptide chain elongation (R-HSA-156902)



**Cellular compartments:** cytosol.

The mechanism of a peptide bond requires the movement of three protons. First the deprotonation of the ammonium ion generates a reactive amine, allowing a nucleophilic attack on the carbonyl group. This is followed by the loss of a proton from the reaction intermediate, only to be taken up by the oxygen on the leaving group (from the end of the amino acid chain bound to the tRNA in the P-site). The peptide bond formation results in the net loss of one water molecule, leaving a deacylated-tRNA in the P-site, and a nascent polypeptide chain one amino acid larger in the A-site.

For the purpose of illustration, the figures used in the section show one amino acid being added to a peptidyl-tRNA with a growing peptide chain.

### References

Lorsch JR & Green R (2002). The path to perdition is paved with protons. *Cell*, 110, 665-8. [🔗](#)

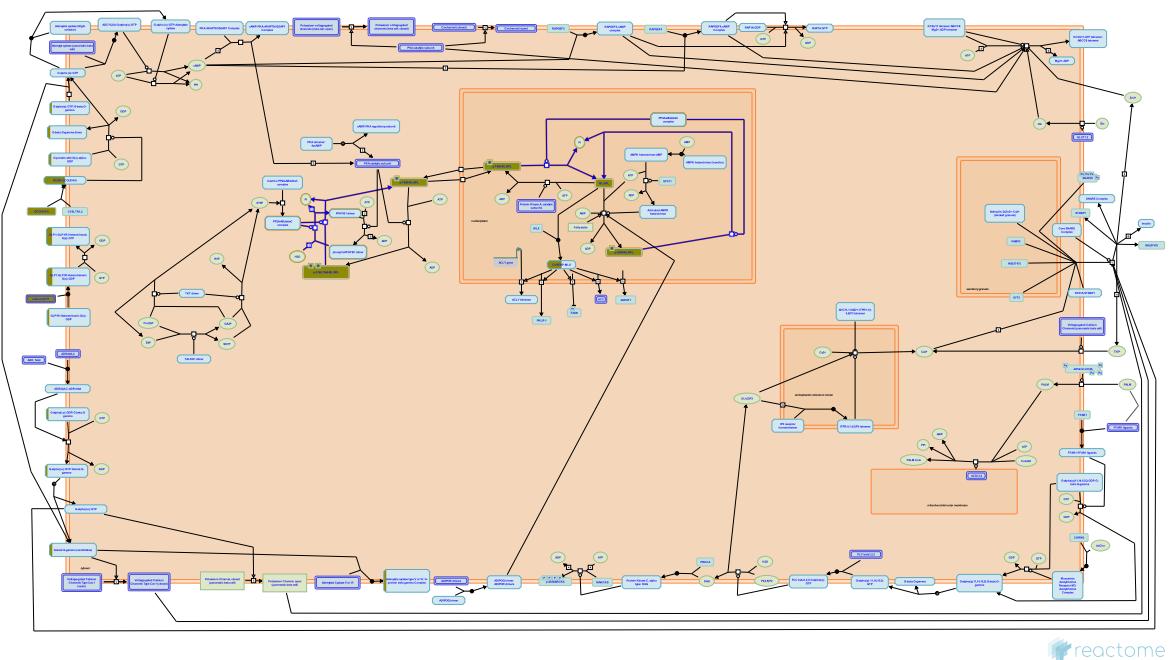
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| 2005-03-13 | Authored | Gopinathrao G                |
| 2005-03-17 | Created  | Balar B, Ulloque R, Kinzy TG |
| 2022-01-09 | Modified | Weiser JD                    |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

### 13. PP2A-mediated dephosphorylation of key metabolic factors (R-HSA-163767)



**Cellular compartments:** nucleoplasm, cytosol.

A member of the PP2A family of phosphatases dephosphorylates both cytosolic and nuclear forms of ChREBP (Carbohydrate Response Element Binding Protein). In the nucleus, dephosphorylated ChREBP complexes with MLX protein and binds to ChRE sequence elements in chromosomal DNA, activating transcription of genes involved in glycolysis and lipogenesis. The phosphatase is activated by Xylulose-5-phosphate, an intermediate of the pentose phosphate pathway (Kabashima et al. 2003). The rat enzyme has been purified to homogeneity and shown by partial amino acid sequence analysis to differ from previously described PP2A phosphatases (Nishimura and Uyeda 1995) - the human enzyme has not been characterized.

### References

Veech RL (2003). A humble hexose monophosphate pathway metabolite regulates short- and long-term control of lipogenesis. Proc Natl Acad Sci U S A, 100, 5578-80. [View](#)

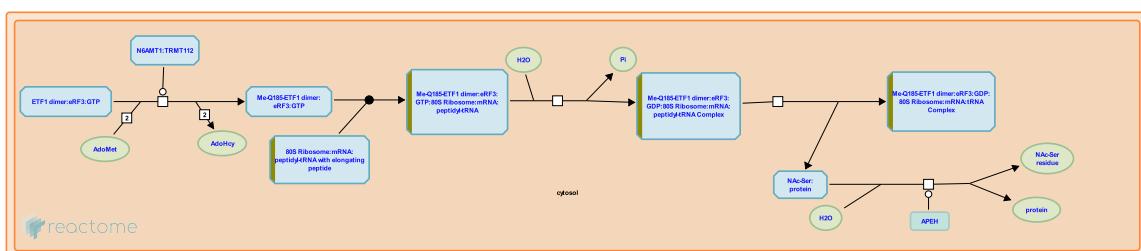
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| 2005-05-06 | Created  | Gopinathrao G |
| 2005-05-13 | Authored | Gopinathrao G |
| 2020-11-10 | Modified | D'Eustachio P |

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

| Input  | UniProt Id |
|--------|------------|
| MLXIPL | Q9NP71     |

## 14. Eukaryotic Translation Termination (R-HSA-72764)



**Cellular compartments:** cytosol.

The arrival of any of the three stop codons (UAA, UAG and UGA) into the ribosomal A-site triggers the binding of a release factor (RF) to the ribosome and subsequent polypeptide chain release. In eukaryotes, the RF is composed of two proteins, eRF1 and eRF3. eRF1 is responsible for the hydrolysis of the peptidyl-tRNA, while eRF3 provides a GTP-dependent function. The ribosome releases the mRNA and dissociates into its two complex subunits, which can reassemble on another molecule to begin a new round of protein synthesis. It should be noted that at present, there is no factor identified in eukaryotes that would be the functional equivalent of the bacterial ribosome release (or recycling) factor, RRF, that catalyzes dissociation of the ribosome from the mRNA following release of the polypeptide

## References

- Salas-Marco J & Bedwell DM (2004). GTP hydrolysis by eRF3 facilitates stop codon decoding during eukaryotic translation termination. *Mol Cell Biol*, 24, 7769-78. [View](#)
- Ichikawa S & Kaji A (1989). Molecular cloning and expression of ribosome releasing factor. *J Biol Chem*, 264, 20054-9. [View](#)

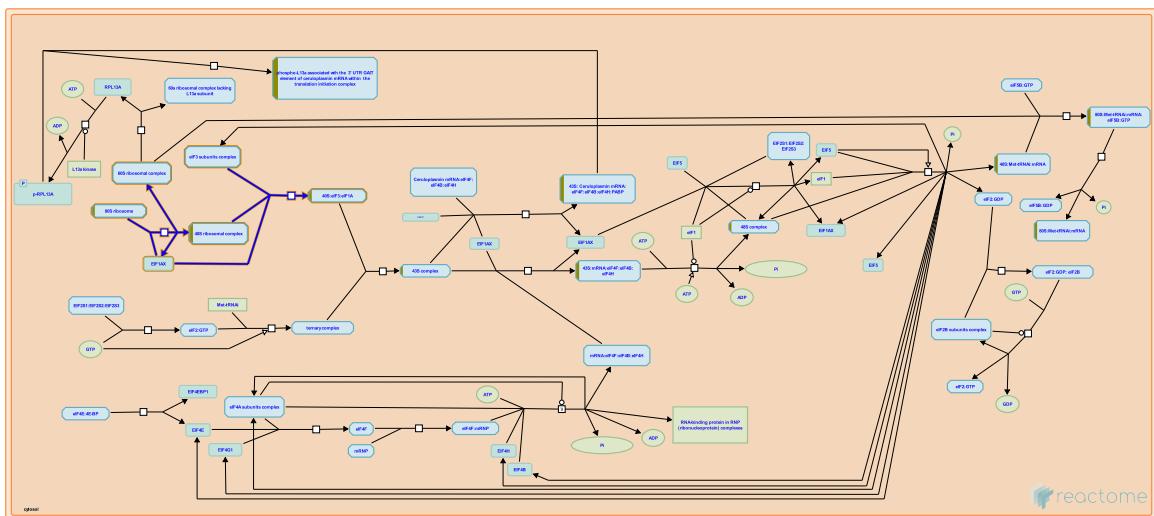
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| 2004-11-09 | Authored | Bedwell DM             |
| 2005-01-03 | Created  | Merrick WC, Bedwell DM |
| 2021-11-23 | Edited   | Gillespie ME           |
| 2022-01-09 | Modified | Weiser JD              |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

## 15. Formation of a pool of free 40S subunits (R-HSA-72689)



**Cellular compartments:** cytosol.

The 80S ribosome dissociates into free 40S (small) and 60S (large) ribosomal subunits. Each ribosomal subunit is constituted by several individual ribosomal proteins and rRNA.

## References

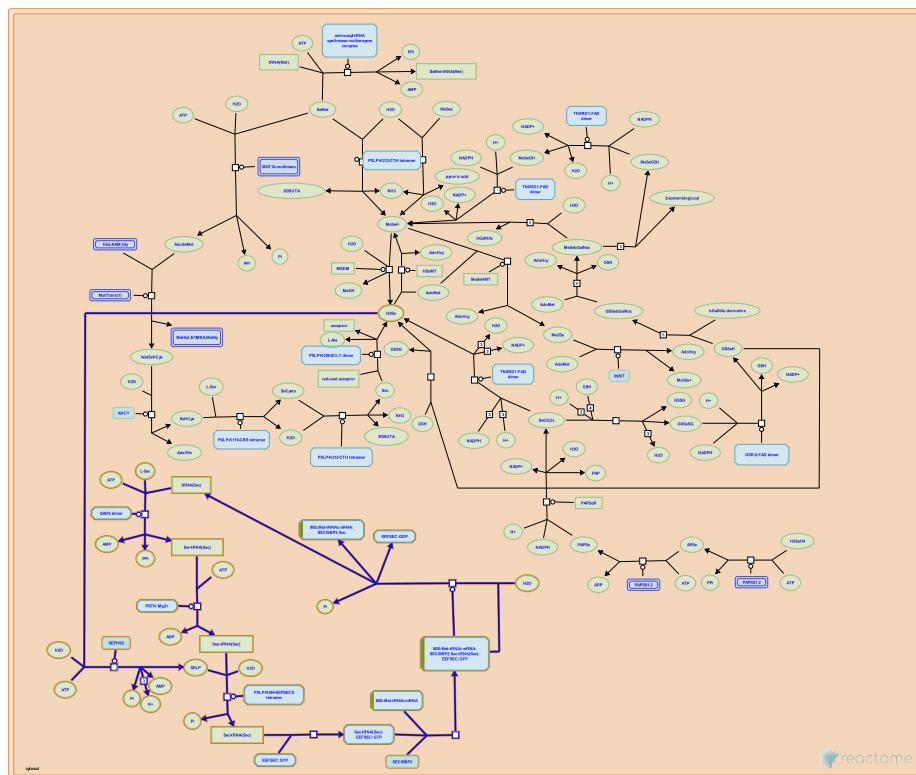
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| 2022-01-09 | Modified | Weiser JD |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

## 16. Selenocysteine synthesis (R-HSA-2408557)



Selenocysteine, the 21st genetically encoded amino acid, is the major form of the antioxidant trace element selenium in the human body. In eukaryotes and archaea its synthesis proceeds through a phosphorylated intermediate in a tRNA-dependent fashion. The final step of selenocysteine formation is catalyzed by O-phosphoseryl-tRNA:selenocysteinyl-tRNA synthase (SEPSECS) that converts phosphoseryl-tRNA(Sec) to selenocysteinyl-tRNA(Sec).

## References

- Donovan J & Copeland PR (2010). Threading the needle: getting selenocysteine into proteins. *Antioxid. Redox Signal.*, 12, 881-92. [🔗](#)
- Palioura S, Herkel J, Simonovic M, Lohse AW & Säfll D (2010). Human SepSecS or SLA/LP: selenocysteine formation and autoimmune hepatitis. *Biol. Chem.*, 391, 771-6. [🔗](#)
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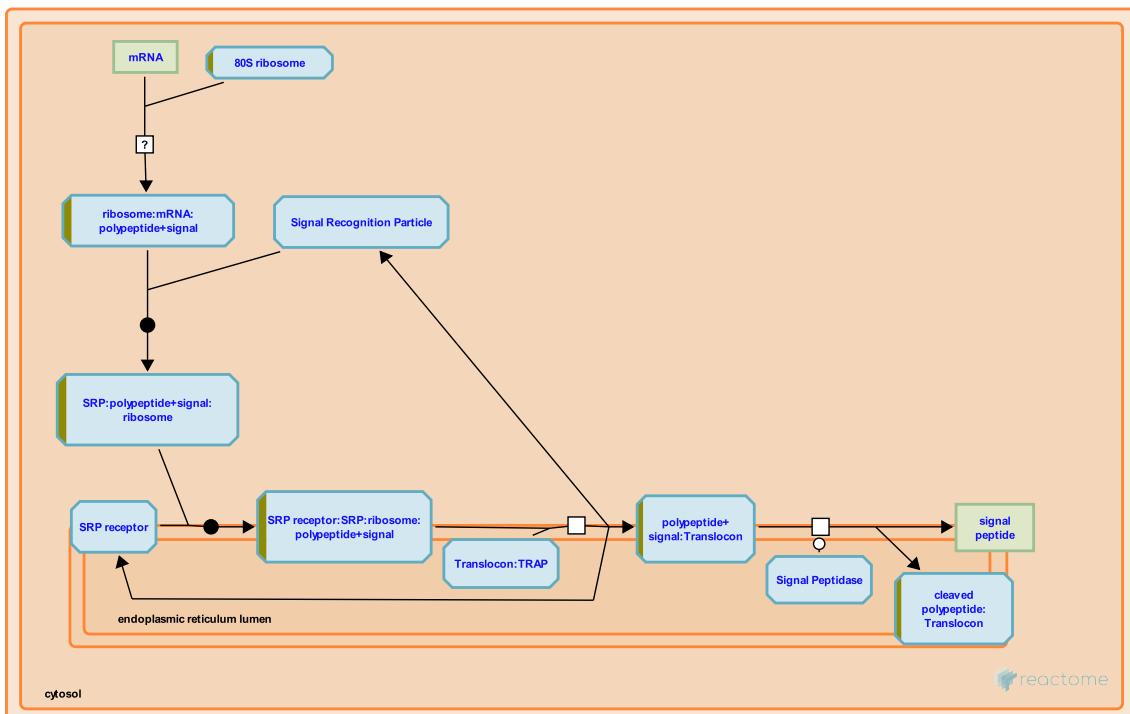
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| 2012-07-17 | Created  | Williams MG   |
| 2014-05-06 | Authored | Williams MG   |
| 2015-08-30 | Edited   | D'Eustachio P |
| 2015-08-30 | Reviewed | Rush MG       |
| 2021-11-28 | Modified | Weiser JD     |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

## 17. SRP-dependent cotranslational protein targeting to membrane (R-HSA-1799339)



**Cellular compartments:** endoplasmic reticulum membrane, endoplasmic reticulum lumen, cytosol.

The process for translation of a protein destined for the endoplasmic reticulum (ER) branches from the canonical cytosolic translation process at the point when a nascent polypeptide containing a hydrophobic signal sequence is exposed on the surface of the cytosolic ribosome:mRNA:peptide complex. The signal sequence mediates the interaction of this complex with a cytosolic signal recognition particle (SRP) to form a complex which in turn docks with an SRP receptor complex on the ER membrane. There the ribosome complex is transferred from the SRP complex to a translocon complex embedded in the ER membrane and reoriented so that the nascent polypeptide protrudes through a pore in the translocon into the ER lumen. Translation, which had been halted by SRP binding, now resumes, the signal peptide is cleaved from the polypeptide, and elongation proceeds, with the growing polypeptide oriented into the ER lumen.

## References

### Edit history

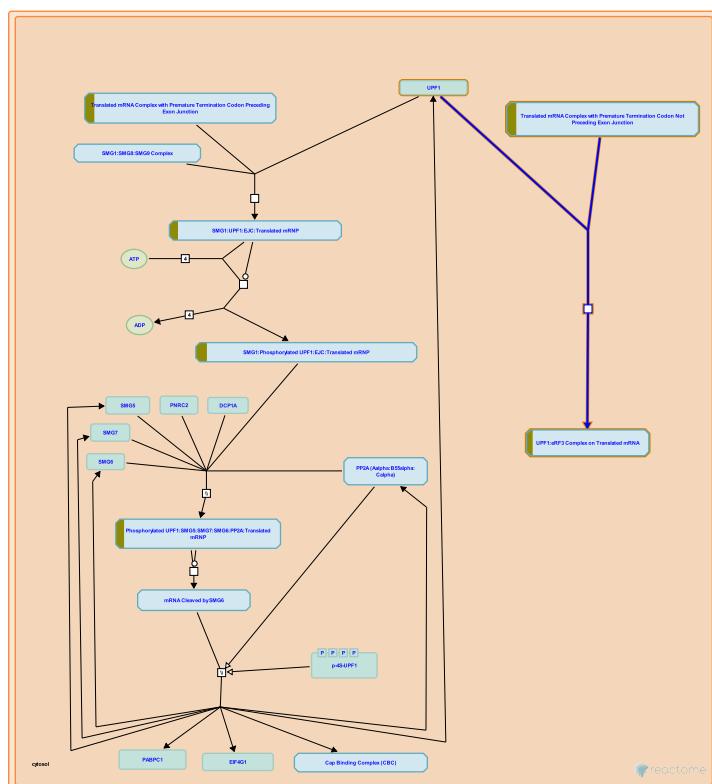
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|------------|----------|---|
| 2008-11-20 | Authored | May B, Gopinathrao G                    |
| 2008-12-02 | Reviewed | Matthews L, Gillespie ME, D'Eustachio P |
| 2011-10-22 | Revised  | D'Eustachio P                           |
| 2011-10-23 | Edited   | D'Eustachio P                           |
| 2011-10-23 | Created  | D'Eustachio P                           |

| Date       | Action   | Author    |
|------------|----------|-----------|
| 2022-01-09 | Modified | Weiser JD |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

## 18. Nonsense Mediated Decay (NMD) independent of the Exon Junction Complex (EJC) (R-HSA-975956)



**Cellular compartments:** cytosol.

Nonsense-mediated decay has been observed with mRNAs that do not have an exon junction complex (EJC) downstream of the termination codon (reviewed in Isken and Maquat 2007, Chang et al. 2007, Behm-Ansmant et al. 2007, Rebbapragada and Lykke-Andersen 2009, Nicholson et al. 2010). In these cases the trigger is unknown but a correlation with the length of the 3' UTR has sometimes been seen. The current model posits a competition between PABP and UPF1 for access to eRF3 at the terminating ribosome (Ivanov et al. 2008, Singh et al. 2008, reviewed in Bhuvanagiri et al. 2010). Abnormally long 3' UTRs may prevent PABP from efficiently interacting with eRF3 and allow UPF1 to bind eRF3 instead. Long UTRs with hairpin loops may bring PABP closer to eRF3 and help evade NMD (Eberle et al. 2008).

The pathway of degradation taken during EJC-independent NMD has not been elucidated. It is thought that phosphorylation of UPF1 by SMG1 and recruitment of SMG6 or SMG5 and SMG7 are involved, as with EJC-enhanced NMD, but this has not yet been shown.

## References

- Yepiskoposyan H, Kleinschmidt N, Zamudio Orozco R, Metze S, Muhlemann O & Nicholson P (2010). Nonsense-mediated mRNA decay in human cells: mechanistic insights, functions beyond quality control and the double-life of NMD factors. *Cell Mol Life Sci*, 67, 677-700. ↗
- Stalder L, Eberle AB, Mathys H, Orozco RZ & Muhlemann O (2008). Posttranscriptional gene regulation by spatial rearrangement of the 3' untranslated region. *PLoS Biol*, 6, e92. ↗

Sauliñ re J, Wittkopp N, Behm-Ansmant I, Izaurrealde E, Rehwinkel J & Kashima I (2007). mRNA quality control: an ancient machinery recognizes and degrades mRNAs with nonsense codons. FEBS Lett, 581, 2845-53. [🔗](#)

Rebbapragada I, Singh G & Lykke-Andersen J (2008). A competition between stimulators and antagonists of Upf complex recruitment governs human nonsense-mediated mRNA decay. PLoS Biol, 6, e111. [🔗](#)

Bhuvanagiri M, Kulozik AE, Hentze MW & Schlitter AM (2010). NMD: RNA biology meets human genetic medicine. Biochem J, 430, 365-77. [🔗](#)

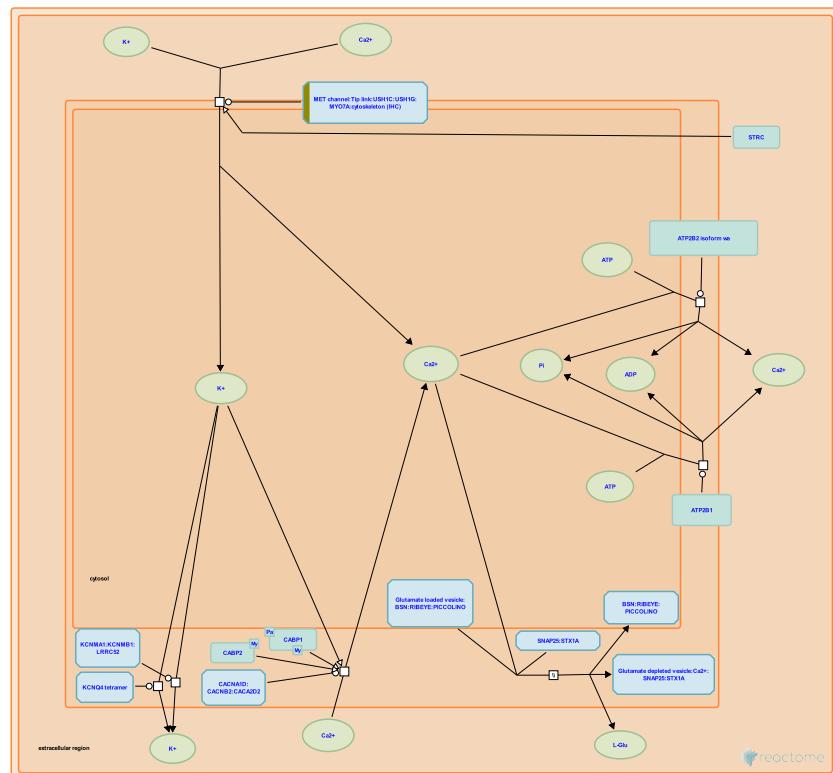
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| 2010-10-08 | Authored | May B       |
| 2010-10-11 | Created  | May B       |
| 2011-05-19 | Reviewed | Neu-Yilik G |
| 2022-01-09 | Modified | Weiser JD   |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

## 19. Sensory processing of sound by inner hair cells of the cochlea (R-HSA-9662360)



Inner hair cells (IHCs) of the cochlea transduce sound waves into an ionic (mainly potassium) current that leads to exocytosis of glutamate from the IHC and activation of postsynaptic type I afferent fibers of the radial ganglion (reviewed in Meyer and Moser 2010, Moser and Vogl 2016, Fettiplace 2017). IHCs have stereocilia on their apical surface that are arranged in rows of increasing height, a "staircase" arrangement. Stereocilia of different rows are connected by a tip link comprising a CDH23 dimer on the taller stereocilium bound to a PCDH15 dimer on the shorter stereocilium. PCDH15 interacts with LHFPL5, an auxiliary subunit of the mechanoelectrical transduction channel (MET channel, also called the mechanotransduction channel), which contains at least TMC1 (adults) or TMC2 (newborns), TMIE, and the auxiliary subunits LHFPL5 and CIB2 (reviewed in Fettiplace and Kim 2014, Fettiplace 2016).

Deflection of the stereocilia by sound waves creates tension on the tip link that increases the open probability of the MET channel, which then transports calcium and potassium ions from the scala media into the IHC, depolarizing the IHC (reviewed in Fettiplace 2017). The potassium channel KCNQ4 located in the neck region of the cell may also participate in depolarization. The depolarization of the IHC opens voltage-gated Cav1.3 channels (CACNA1D:CACA2D2:CACNB2) located in stripes near ribbon synapses on the basolateral surface of the IHC. The resulting localized influx of calcium ions activates exocytosis of glutamate into the synapse by an interaction between calcium and Otoferlin (OTOF) on glutamate-loaded vesicles in the IHC (reviewed in Wichmann 2015).

Ribbon synapses are characterized by a multiprotein complex, the ribbon, that contains at least BASSOON, RIBEYE (an isoform of CTBP2), and PICCOLINO (a small isoform of PICCOLO) and appears to act to transiently tether vesicles near the synapse and thereby increase the pool of readily releasable vesicles (reviewed in Safieddine et al. 2012, Wichman and Moser 2015, Pangrsic and Vogl 2018, Moser et al. 2020).

ATP2B1 calcium channels, ATP2B2 calcium channels, KCNMA1:KCNMB1:LRRC52 potassium channels, and basolateral KCNQ4 potassium channels transport cations out of the IHC and thereby act to repolarize the cell and limit the duration of the synaptic potentials (reviewed in Patuzzi 2011, Oak and Yi 2014).

## References

- Wichmann C (2015). Molecularly and structurally distinct synapses mediate reliable encoding and processing of auditory information. *Hear. Res.*, 330, 178-90. [🔗](#)
- Moser T & Vogl C (2016). New insights into cochlear sound encoding. *F1000Res*, 5. [🔗](#)
- Fettiplace R (2016). Is TMC1 the Hair Cell Mechanotransducer Channel?. *Biophys. J.*, 111, 3-9. [🔗](#)
- Oak MH & Yi E (2014). Voltage-gated K(+) channels contributing to temporal precision at the inner hair cell-auditory afferent nerve fiber synapses in the mammalian cochlea. *Arch. Pharm. Res.*, 37, 821-33. [🔗](#)
- Kim KX & Fettiplace R (2014). The physiology of mechanoelectrical transduction channels in hearing. *Physiol. Rev.*, 94, 951-86. [🔗](#)

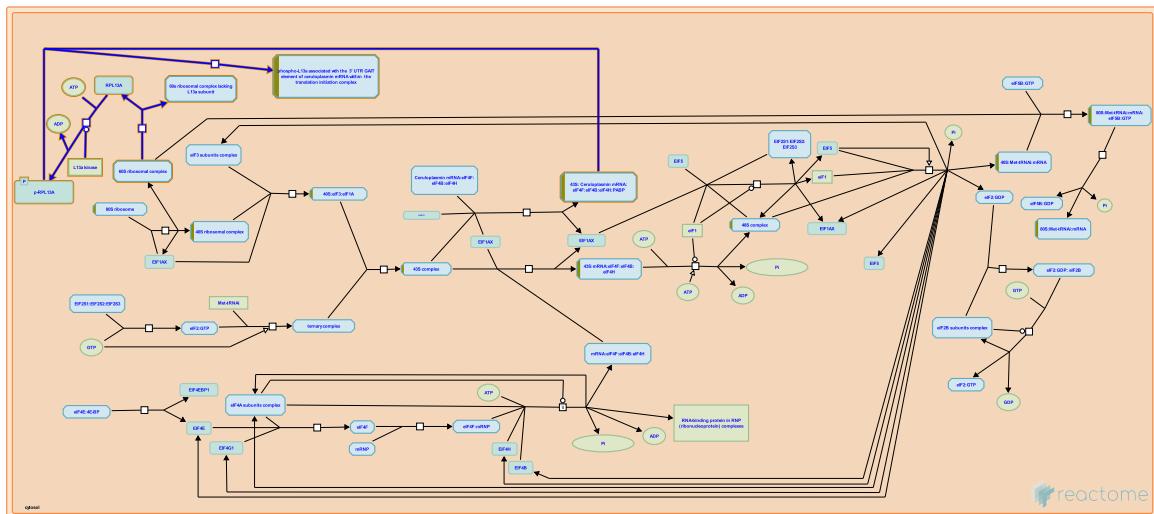
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| 2019-09-23 | Edited   | May B      |
| 2019-09-23 | Authored | May B      |
| 2019-09-23 | Created  | May B      |
| 2020-09-14 | Reviewed | Furness DN |
| 2020-12-12 | Modified | May B      |

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

| Input   | UniProt Id | Input | UniProt Id |
|---------|------------|-------|------------|
| EPB41L3 | Q9Y2J2     | USH1C | Q9Y6N9     |

## 20. L13a-mediated translational silencing of Ceruloplasmin expression (R-HSA-156827)



**Cellular compartments:** cytosol.

While circularization of mRNA during translation initiation is thought to contribute to an increase in the efficiency of translation, it also appears to provide a mechanism for translational silencing. This might be achieved by bringing inhibitory 3' UTR-binding proteins into a position in which they interfere either with the function of the translation initiation complex or with the assembly of the ribosome (Mazumder et al 2001). Translational silencing of Ceruloplasmin (Cp) occurs 16 hrs after its induction by INF-gamma (Mazumder et al., 1997). Although the mechanism by which silencing occurs has not yet been determined, this process is mediated by the L13a subunit of the 60s ribosome and thought to require circularization of the Cp mRNA (Sampath et al., 2003; Mazumder et al., 2001; Mazumder et al., 2003). Between 14 and 16 hrs after INF gamma induction, the L13a subunit of the 60s ribosome is phosphorylated and released from the 60s subunit. Phosphorylated L13a then associates with the GAIT element in the 3' UTR of the Cp mRNA inhibiting its translation.

### References

Seshadri V, Sampath P, DiCorleto PE, Maitra RK, Fox PL & Mazumder B (2003). Regulated release of L13a from the 60S ribosomal subunit as a mechanism of transcript-specific translational control . Cell, 115, 187-98. [\[link\]](#)

### Edit history

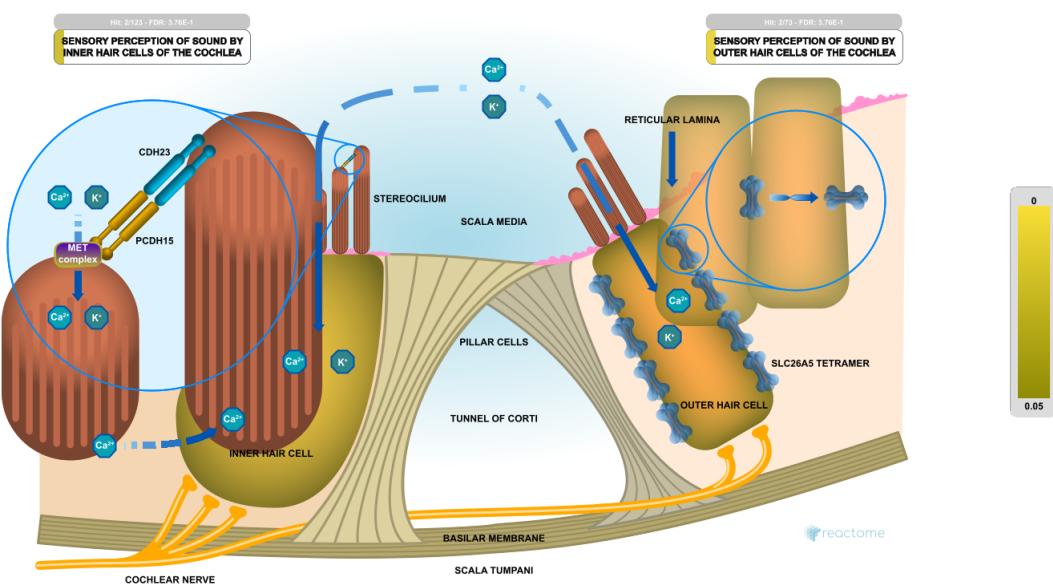
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| 2004-12-13 | Authored | Matthews L |
| 2004-12-20 | Created  | Gebauer F  |
| 2013-11-25 | Edited   | Matthews L |
| 2022-01-09 | Modified | Weiser JD  |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

| Input | UniProt Id |
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|-------|------------|

## 21. Sensory processing of sound ([R-HSA-9659379](#))



In mammals, sounds are processed in the cochlea, a spiral-shaped organ in the inner ear (reviewed in Basch et al. 2016, Fettiplace 2017, Koppl and Manley 2019). Low frequency sounds are sensed at the distal end (apex) of the cochlea; high frequency sounds are sensed at the proximal end (base) of the cochlea (reviewed in Dallos 1992, Manley 2018). Sound vibrations are transmitted from the eardrum through the three bones of the inner ear (malleus, incus, stapes) and the oval window of the cochlea to the fluids within the cochlea. Within the organ of Corti in the cochlea there are 3 rows of outer hair cells (OHCs) on the external side of the tunnel of Corti and 1 row of inner hair cells (IHCs) on the internal side (Spoendlin 1967). Each IHC synapses with approximately 20 afferent myelinated type I spiral ganglion neurons and functions as a sensory receptor to convert the energy of sound waves to secretion of glutamate neurotransmitter. Multiple OHCs synapse with each unmyelinated type II afferent neuron and OHCs are also synapsed with efferent medial olivocochlear fibers (Spoendlin 1967). The primary function of OHCs, however, is amplification of organ of Corti motions in response to sound (Ryan and Dallos 1975). Amplification is produced by changes in receptor-potential driven cell length caused by changes in the conformation of the unusual membrane protein prestin (SLC26A5, Zheng et al. 2000).

IHCs and OHCs sense the sonic vibrations by deflection of stereocilia on their apical surfaces (reviewed in Fettiplace et al. 2017, McPherson 2018). The stereocilia are arranged in rows of increasing height, with a stereocilium of one row connected to a stereocilium of another row by a tip link composed of a CDH23 dimer on the taller stereocilium joined at its N-termini to the N-termini of a PCDH15 dimer on the shorter stereocilium. CDH23 is connected to the cytoskeleton of the taller stereocilium via MYO7A (MyoVIIa), USH1C (Harmonin), and USH1G (Sans) (reviewed in Peng et al. 2011, Cosgrove and Zallocchi 2014, Barr-Gillespie 2015, Fettiplace 2017, McGrath et al. 2017, Cunningham and Mäller 2019, Maoiléidigh and Ricci 2019, Velez-Ortega and Frolenkov 2019) while PCDH15 on the shorter stereocilium interacts with LHFPL5, an auxiliary subunit of the mechanoelectrical transduction channel (MET channel, also known as the mechanotransduction channel), which contains at least TMC1 or TMC2, TMIE, and the auxiliary subunits LHFPL5 and CIB2 (reviewed in Fettiplace 2016, Qiu and Mäller 2018, Corey et al. 2019). Deflection of stereocilia in the direction that increases tension on the tip link causes depolarization of the cell by increasing the open probability of the MET channel, which then transports calcium and potassium into the hair cell according to the gradient of those ions between the scala media (containing endolymph at 154 mM K<sup>+</sup> and <1 mM Ca<sup>2+</sup>) at the apex of the cell and the scala tympani (containing perilymph at 7 mM K<sup>+</sup>) at the base (reviewed in Fettiplace and Kim 2014). Similarly, compression of the tip link by deflection of the stereocilia in the opposite direction decreases the open probability of the MET channel and causes hyperpolarization of the cell.

Depolarization of IHCs causes opening of voltage-gated calcium channels arrayed in stripes on the basolateral membrane close to ribbon synapses formed between the IHC and the afferent fiber of a myelinated type I spiral ganglion neuron. This results in a localized increase in cytosolic calcium ions which interact with Otoferlin (OTOF) on glutamate-containing synaptic vesicles at the ribbon structure to activate exocytosis of glutamate into the synapse formed with the afferent neuron (reviewed in Wichmann 2015, Pangrsic and Vogl 2018). Ribbon synapses are distinguished by electron-dense ribbon structures projecting from the presynaptic membrane into the cytosol and comprising at least BASSOON, RIBEYE (an isoform of CTBP2), and PICCOLINO (an isoform of PICCOLO). The ribbon structures appear to transiently bind synaptic vesicles and facilitate resupply of synaptic vesicles at active zones to refill the pool of readily releasable vesicles (reviewed in Moser et al. 2006, Moser et al. 2020).

In contrast with IHCs, OHCs mainly function in sound amplification by decreasing up to about 4% in length in response to depolarization caused by opening of the MET channel and increasing in length in response to hyperpolarization caused by channel closing, resulting in alternating compression and decompression between the reticular lamina and the basilar membrane. The changes in the length of the OHC are caused by very rapid (microseconds), voltage-sensitive changes in the conformation of the membrane protein prestin (SLC26A5). Stereociliary ATP2B2 (PMCA2) extrudes calcium ions and basally located KCNQ4 extrudes potassium ions to repolarize the OHC.

OHCs are synapsed with efferent cholinergic medial olivocochlear fibers (reviewed in Fritzsch and Elliott 2017, Fuchs and Lauer 2019). Acetylcholine released at the synapse binds an unusual, nicotine-antagonized, nicotinic receptor comprising CHRNA9 and CHRNA10. Upon binding acetylcholine, CHRNA9:CHRNA10 transports calcium ions into the OHC. The calcium activates SK2 potassium channels (KCNN2) and BK potassium channels (KCNMA1:KCNMB1) which extrude potassium ions, hyperpolarize the OHC, and inhibit activation of the OHC.

Loud sounds can cause a temporary threshold shift (temporary loss of hearing) caused by damage to stereocilia and synapses or permanent threshold shift (permanent loss of hearing) caused by damage or death of hair cells and neurons (reviewed in Kurabi et al. 2017).

## References

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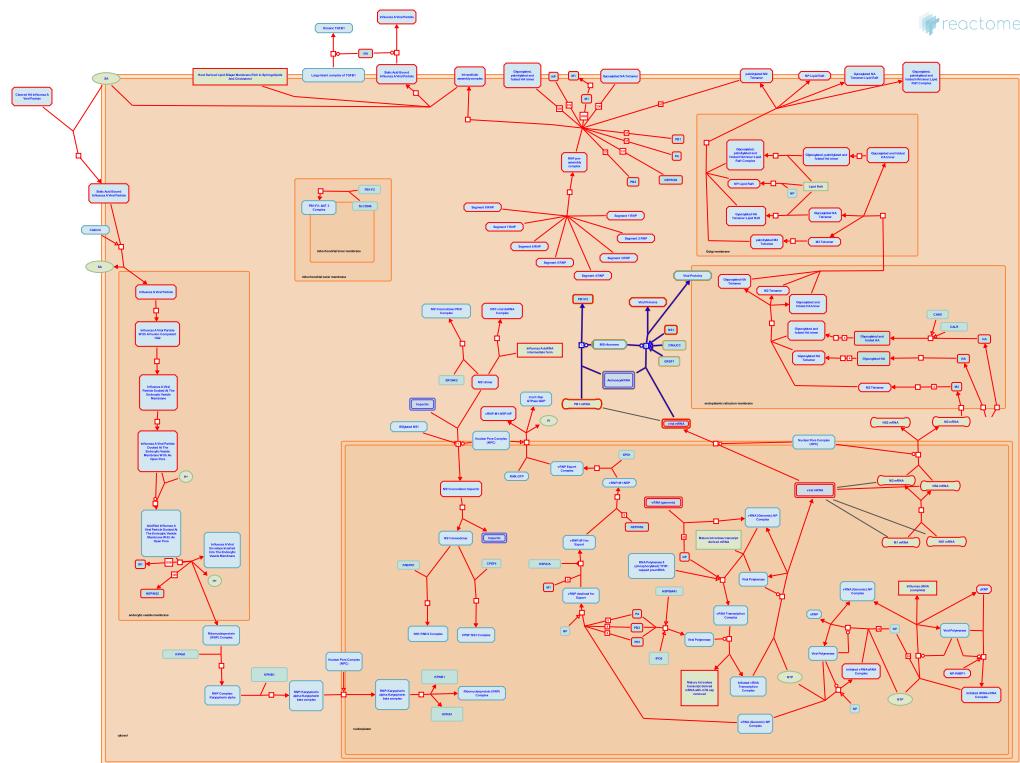
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| Date       | Action   | Author     |
|------------|----------|------------|
| 2019-08-27 | Edited   | May B      |
| 2019-08-27 | Authored | May B      |
| 2019-08-27 | Created  | May B      |
| 2020-09-14 | Reviewed | Furness DN |
| 2021-03-04 | Modified | Shorser S  |

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

| Input   | UniProt Id | Input | UniProt Id |
|---------|------------|-------|------------|
| EPB41L3 | Q9Y2J2     | USH1C | Q9Y6N9     |

## 22. Viral mRNA Translation (R-HSA-192823)



**Cellular compartments:** cytosol.

**Diseases:** influenza.

Spliced and unspliced viral mRNA in the cytoplasm are translated by host cell ribosomal translation machinery (reviewed in Kash, 2006). At least ten viral proteins are synthesized: HA, NA, PB1, PB2, PA, NP, NS1, NEP/NS2, M1, and M2. Viral mRNA translation is believed to be enhanced by conserved 5'UTR sequences that interact with the ribosomal machinery and at least one cellular RNA-binding protein, G-rich sequence factor 1 (GRSF-1), has been found to specifically interact with the viral 5' UTRs. (Park, 1995; Park, 1999). The viral NS1 protein and the cellular protein P58(IPK) enhance viral translation indirectly by preventing the activation of the translational inhibitor PKR (Salvatore, 2002; Goodman, 2006). The viral NS1 protein has also been proposed to specifically enhance translation through interaction with host poly(A)-binding protein 1 (PABP1) (Burgui, 2003). Simultaneously, host cell protein synthesis is downregulated in influenza virus infection through still uncharacterized mechanisms (Katze, 1986; Garfinkel, 1992; Kash, 2006). In most human influenza A strains (such as PR8), the PB1 mRNA segment is capable of producing a second protein, PB1-F2, from a short +1 open reading frame initiating downstream of the PB1 ORF initiation codon (Chen, 2001).

## References

Korth MJ, Katze MG, Kash JC & Goodman AG (2006). Hijacking of the host-cell response and translational control during influenza virus infection. *Virus Res*, 119, 111-20. ↗

## Edit history

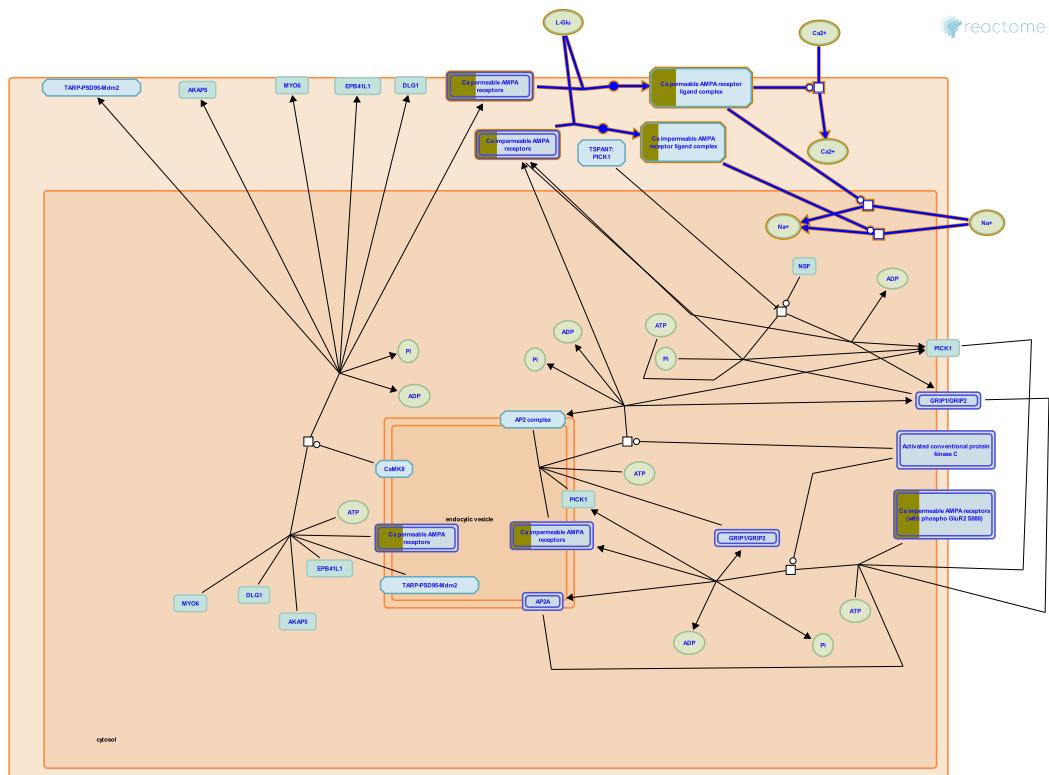
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|------------|---------|--------------|
| 2007-02-07 | Created | Gillespie ME |

| Date       | Action   | Author                   |
|------------|----------|--------------------------|
| 2007-02-13 | Reviewed | Squires B                |
| 2007-02-13 | Authored | Garcia-Sastre A, Bortz E |
| 2022-01-09 | Modified | Weiser JD                |

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

| Input  | UniProt Id     |
|--------|----------------|
| RPS4Y1 | P22090, Q8TD47 |

## 23. Activation of AMPA receptors (R-HSA-399710)



**Cellular compartments:** plasma membrane, extracellular region.

AMPA receptors are functionally either Ca permeable or Ca impermeable based on the subunit composition. Ca permeability is determined by GluR2 subunit which undergoes post-transcriptional RNA editing that changes glutamine (Q) at the pore to arginine (R). Incorporation of even a single subunit in the AMPA receptor confers Ca-limiting properties. Ca permeable AMPA receptors permit Ca and Na whereas Ca impermeable AMPA receptors permit only Na. In general, glutamatergic neurons contain Ca impermeable AMPA receptors and GABAergic interneurons contain Ca permeable AMPA receptors. However, some synapses do contain a mixture of Ca permeable and Ca impermeable AMPA receptors. GluR1-4 are encoded by four genes however, alternative splicing generates several functional subunits namely long and short forms of GluR1 and GluR2. GluR4 has long tail only and GluR3 has short tail only. Besides the differences in the tail length, flip/flop isoforms are generated by an interchangeable exon that codes the fourth membranous domain towards the C terminus. The flip/flop isoforms determine rate of desensitization/resensitization and the rate of channel closing. Receptors homomers or heteromers assembled from the combination of GluR1-4 subunits that vary in C tail length and flip/flop versions generates a whole battery of functionally distinct AMPA receptors.

## References

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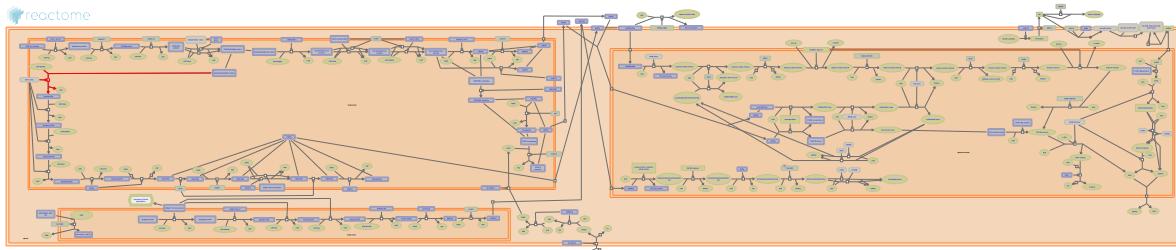
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| 2008-01-14 | Edited   | Mahajan SS |
| 2008-01-14 | Authored | Mahajan SS |
| 2009-03-19 | Created  | Mahajan SS |
| 2009-05-15 | Reviewed | Ziff EB    |
| 2022-01-09 | Modified | Weiser JD  |

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

| Input | UniProt Id |
|-------|------------|
| GRIA3 | P42263     |

## 24. Defective EXT1 causes exostoses 1, TRPS2 and CHDS (R-HSA-3656253)



**Diseases:** hereditary multiple exostoses.

Heparan sulfate (HS) is involved in regulating various body functions during development, homeostasis and pathology including blood clotting, angiogenesis and metastasis of cancer cells. Exostosin 1 and 2 (EXT1 and 2) glycosyltransferases are required to form HS. They are able to transfer N-acetylglicosamine (GlcNAc) and glucuronate (GlcA) to HS during its synthesis. The functional form of these enzymes appears to be a complex of the two located on the Golgi membrane. Defects in either EXT1 or EXT2 can cause hereditary multiple exostoses 1 (Petersen 1989) and 2 (McGaughran et al. 1995) respectively (MIM:133700 and MIM:133701), autosomal dominant disorders characterized by multiple projections of bone capped by cartilage resulting in deformed legs, forearms and hands. Trichorhinophalangeal syndrome, type II (TRPS2 aka Langer-Giedion syndrome, LGS) is a disorder that combines the clinical features of trichorhinophalangeal syndrome type I (TRPS1, MIM:190350) and multiple exostoses type I, caused by mutations in the TRPS1 and EXT1 genes, respectively (Langer et al. 1984, Ludecke et al. 1995). Defects in EXT1 may also be responsible for chondrosarcoma (CHDS; MIM:215300) (Schajowicz & Bessone 1967, Hecht et al. 1995).

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## Edit history

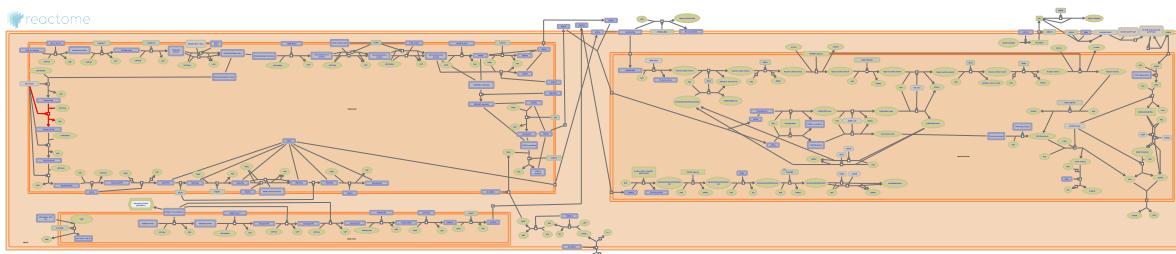
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| 2013-05-31 | Authored | Jassal B    |
| 2013-05-31 | Created  | Jassal B    |
| 2014-07-09 | Reviewed | Spillmann D |

| Date       | Action   | Author   |
|------------|----------|----------|
| 2018-01-31 | Modified | Jassal B |

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

| Input | UniProt Id |
|-------|------------|
| GPC6  | Q9Y625     |

## 25. Defective EXT2 causes exostoses 2 (R-HSA-3656237)



**Diseases:** hereditary multiple exostoses.

Heparan sulfate (HS) is involved in regulating various body functions during development, homeostasis and pathology including blood clotting, angiogenesis and metastasis of cancer cells. Exostosin 1 and 2 (EXT1 and 2) glycosyltransferases are required to form HS. They are able to transfer N-acetylglucosamine (GlcNAc) and glucuronate (GlcA) to HS during its synthesis. The functional form of these enzymes appears to be a complex of the two located on the Golgi membrane. Defects in either EXT1 or EXT2 can cause hereditary multiple exostoses 1 (Petersen 1989) and 2 (McGaughran et al. 1995) respectively (MIM:133700 and MIM:133701), autosomal dominant disorders characterised by multiple projections of bone capped by cartilage resulting in deformed legs, forearms and hands.

## References

- Peterson HA (1989). Multiple hereditary osteochondromata. Clin. Orthop. Relat. Res., 222-30. [View](#)
- Evans DG, McGaughran JM & Ward HB (1995). WAGR syndrome and multiple exostoses in a patient with del(11)(p11.2p14.2). J. Med. Genet., 32, 823-4. [View](#)

## Edit history

| Date       | Action   | Author      |
|------------|----------|-------------|
| 2013-05-31 | Edited   | Jassal B    |
| 2013-05-31 | Authored | Jassal B    |
| 2013-05-31 | Created  | Jassal B    |
| 2014-07-09 | Reviewed | Spillmann D |
| 2018-01-31 | Modified | Jassal B    |

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

| Input | UniProt Id |
|-------|------------|
| GPC6  | Q9Y625     |

## 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.

**23 of the submitted entities were found, mapping to 29 Reactome entities**

| Input   | UniProt Id     | Input  | UniProt Id     | Input  | UniProt Id |
|---------|----------------|--------|----------------|--------|------------|
| CAPNS1  | P04632, Q96L46 | CBX6   | O95503         | CECR1  | Q9NZK5     |
| EPB41L3 | Q9Y2J2         | FBXW4  | P57775         | GCG    | P01275     |
| GNB2    | P62879         | GPC6   | Q9Y625         | GRIA3  | P42263     |
| LSAMP   | Q13449         | MLXIPL | Q9NP71         | NPC1L1 | Q9UHC9-2   |
| PCSK2   | P16519         | PDK4   | Q16654         | PI4KA  | P42356     |
| PKD1    | P98161         | RPS4Y1 | P22090, Q8TD47 | SCARB1 | Q8WTW0-2   |
| SMPD1   | P17405         | TXNIP  | Q9H3M7         | USH1C  | Q9Y6N9     |
| WDR59   | Q6PJI9         | WNT4   | O96014, P56705 |        |            |

| Input | Ensembl Id      | Input | Ensembl Id      |
|-------|-----------------|-------|-----------------|
| GCG   | ENSG00000115263 | WNT4  | ENSG00000162552 |

### Interactors (15)

| Input    | UniProt Id | Interacts with | Input    | UniProt Id | Interacts with |
|----------|------------|----------------|----------|------------|----------------|
| C19orf63 | Q5UCC4     | Q8N4V1         | CAPNS1   | P04632     | P20936         |
| CBX6     | O95503     | P11940         | EPB41L3  | Q9Y2J2     | P49841         |
| FBXW4    | P57775     | P63208         | GCG      | P01275     | P01275, P48546 |
| GNB2     | P62879     | P61081         | KIAA1324 | Q6UXG2-3   | P07196         |
| LSAMP    | Q13449     | Q13352         | PI4KA    | P42356     | P19320         |
| PKD1     | Q15139     | P02795         | SCARB1   | Q8WTW0-2   | P02649         |
| TXNIP    | Q9H3M7     | P10599         | USH1C    | Q9Y6N9-4   | P54646         |
| WDR59    | Q6PJI9     | P55735         |          |            |                |

## 7. Identifiers not found

These 4 identifiers were not found neither mapped to any entity in Reactome.

FEV

GPR64

KIAA1244

SNX29