Pathway Analysis Report

Under GSE vs C (224)

This report contains the pathway analysis results for the submitted sample 'Under GSE vs C (224)'. Analysis was performed against Reactome version 78 on 03/11/2021. The web link to these results is:

https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTExMDMwOTU0MTlfMzIzNzA%3D

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

Table of Contents

1. Introduction

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

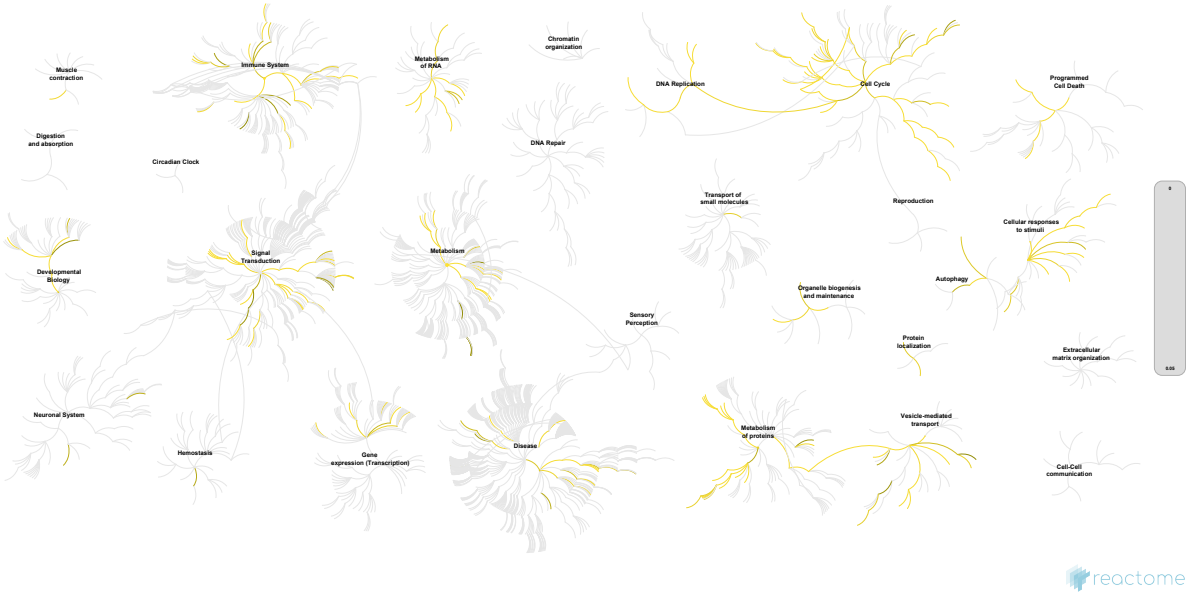
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, … D'Eustachio P (2016). The reactome pathway knowledgebase. Nucleic Acids Research, 44(D1), D481–D487. https://doi.org/10.1093/nar/gkv1351.

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.
- 194 out of 223 identifiers in the sample were found in Reactome, where 841 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMTExMDMwOTU0MTlfMzIzNzA%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
Neutrophil degranulation	37 / 480	0.034	5.39e-13	4.87e-10	9 / 10	7.37e-04
Gene and protein expression by JAK-STAT signaling after Interleukin-12 stimulation	16 / 73	0.005	1.40e-12	6.31e-10	8 / 36	0.003
Interleukin-12 signaling	16 / 84	0.006	1.10e-11	3.32e-09	8 / 56	0.004
Interleukin-12 family signaling	16 / 96	0.007	7.64e-11	1.72e-08	8 / 114	0.008
Axon guidance	34 / 585	0.041	7.23e-09	1.15e-06	39 / 298	0.022
The citric acid (TCA) cycle and respiratory electron transport	21 / 238	0.017	7.66e-09	1.15e-06	35 / 67	0.005
Pyruvate metabolism and Citric Acid (TCA) cycle	14 / 100	0.007	1.05e-08	1.32e-06	18 / 36	0.003
Cellular responses to stress	45 / 952	0.067	1.18e-08	1.32e-06	49 / 381	0.028
Cellular responses to stimuli	45 / 970	0.068	2.04e-08	2.04e-06	49 / 412	0.03
Nervous system development	34 / 621	0.044	3.05e-08	2.74e-06	41 / 324	0.024
Metabolism of RNA	38 / 783	0.055	9.77e-08	8.02e-06	53 / 187	0.014
Prefoldin mediated transfer of substrate to CCT/TriC	8 / 29	0.002	1.08e-07	8.11e-06	2 / 2	1.47e-04
Formation of tubulin folding intermediates by CCT/TriC	8 / 30	0.002	1.39e-07	9.21e-06	2 / 2	1.47e-04
Signaling by ROBO receptors	19 / 235	0.016	1.53e-07	9.21e-06	6 / 60	0.004
AUF1 (hnRNP D0) binds and destabilizes mRNA	10 / 56	0.004	1.54e-07	9.21e-06	4 / 4	2.95e-04
Programmed Cell Death	19 / 238	0.017	1.86e-07	1.04e-05	14 / 197	0.015
Folding of actin by CCT/TriC	6 / 13	9.11e-04	2.27e-07	1.20e-05	2 / 2	1.47e-04
Regulation of mRNA stability by proteins that bind AU-rich elements	12 / 93	0.007	2.82e-07	1.41e-05	7 / 26	0.002
Regulation of expression of SLITs and ROBOs	16 / 183	0.013	5.47e-07	2.57e-05	3 / 20	0.001
Glucose metabolism	14 / 140	0.01	6.00e-07	2.60e-05	16 / 50	0.004
Citric acid cycle (TCA cycle)	9 / 50	0.004	6.05e-07	2.60e-05	11 / 17	0.001
Cooperation of Prefoldin and TriC/CCT in actin and tubulin folding	8 / 37	0.003	6.67e-07	2.63e-05	6 / 6	4.42e-04
Gluconeogenesis	10 / 66	0.005	6.74e-07	2.63e-05	9 / 26	0.002
Apoptosis	16 / 192	0.013	1.02e-06	3.76e-05	10 / 141	0.01

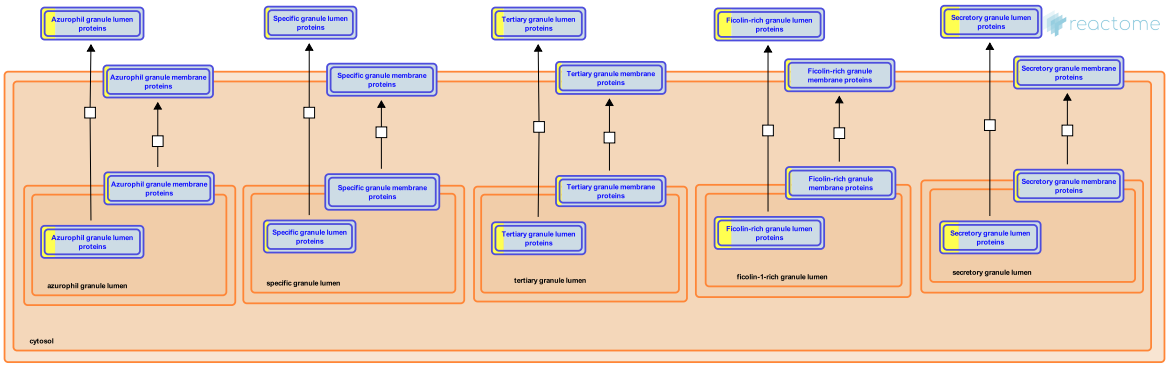
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
COPI-mediated anterograde transport	12 / 107	0.007	1.20e-06	4.09e-05	10 / 12	8.84e-04

* 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. Neutrophil degranulation (R-HSA-6798695)



Neutrophils are the most abundant leukocytes (white blood cells), indispensable in defending the body against invading microorganisms. In response to infection, neutrophils leave the circulation and migrate towards the inflammatory focus. They contain several subsets of granules that are mobilized to fuse with the cell membrane or phagosomal membrane, resulting in the exocytosis or exposure of membrane proteins. Traditionally, neutrophil granule constituents are described as antimicrobial or proteolytic, but granules also introduce membrane proteins to the cell surface, changing how the neutrophil responds to its environment (Borregaard et al. 2007). Primed neutrophils actively secrete cytokines and other inflammatory mediators and can present antigens via MHC II, stimulating T-cells (Wright et al. 2010).

Granules form during neutrophil differentiation. Granule subtypes can be distinguished by their content but overlap in structure and composition. The differences are believed to be a consequence of changing protein expression and differential timing of granule formation during the terminal processes of neutrophil differentiation, rather than sorting (Le Cabec et al. 1996).

The classical granule subsets are Azurophil or primary granules (AG), secondary granules (SG) and gelatinase granules (GG). Neutrophils also contain exocytosable storage cell organelles, storage vesicles (SV), formed by endocytosis they contain many cell-surface markers and extracellular, plasma proteins (Borregaard et al. 1992). Ficolin-1-rich granules (FG) are like GGs highly exocytosable but gelatinase-poor (Rorvig et al. 2009).

References

Wright HL, Moots RJ, Bucknall RC & Edwards SW (2010). Neutrophil function in inflammation and inflammatory diseases. Rheumatology (Oxford), 49, 1618-31.

Borregaard N, Sørensen OE & Theilgaard-Mönch K (2007). Neutrophil granules: a library of innate immunity proteins. Trends Immunol., 28, 340-5.

Rørvig S, Østergaard O, Heegaard NH & Borregaard N (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. J. Leukoc. Biol., 94, 711-21.

Borregaard N, Kjeldsen L, Rygaard K, Bastholm L, Nielsen MH, Sengeløv H, ... Johnsen AH (1992). Stimulus-dependent secretion of plasma proteins from human neutrophils. J. Clin. Invest., 90, 86-96.

Le Cabec V, Cowland JB, Calafat J & Borregaard N (1996). Targeting of proteins to granule subsets is determined by timing and not by sorting: The specific granule protein NGAL is localized to azurophil granules when expressed in HL-60 cells. Proc. Natl. Acad. Sci. U.S.A., 93, 6454-7.

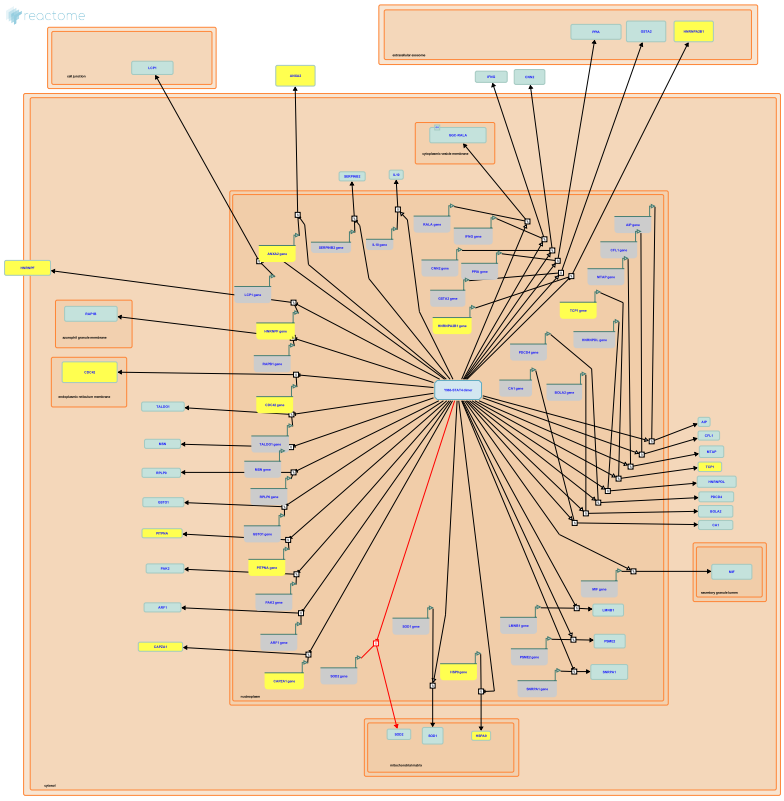
Edit history

Date	Action	Author
2015-09-21	Authored	Jupe S
2015-09-21	Created	Jupe S
2016-06-13	Edited	Jupe S
2016-06-13	Reviewed	Heegaard N
2021-09-10	Modified	Weiser JD

Entities found in this pathway (38)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Acly	P53396	Ahsg	P02765	Anxa2	P07355
Aprt	P07741	Asah1	Q13510	B2m	P61769
Cand1	Q86VP6	Cap1	Q01518	Capn1	P07384
Cct2	P78371	Cct8	P50990	Copb1	P53618
Cpne3	O75131	Csnk2b	P67870	Ctsa	P10619
Ctsc	P53634	Dbnl	Q9UJU6	Dync1h1	Q14204
Eef1a1	P68104	Fth1	P02794	Gdi1	P50395
Gdi2	P50395	Gpi	P06744	Hspa8	P11142
Idh1	O75874	Iqgap1	P46940	Kpnb1	Q14974
Nme2	P22392	Pdxk	O00764	Pgm1	P36871
Pkm	P14618	Psma2	P25787	Psmc3	P17980
Pycard	Q9ULZ3	S100a11	P31949	Serpinb1a	P30740
Tubb4b	P68371	Txndc5	Q8NBS9		

2. Gene and protein expression by JAK-STAT signaling after Interleukin-12 stimulation (R-HSA-8950505)



Cellular compartments: nucleoplasm.

Experiments using human cord blood CD4(+) T cells show 22 protein spots and 20 protein spots, up-regulated and downregulated proteins respectively, following Interleukin-12 stimulation (Rosengren et.al, 2005).
The identified upregulated proteins are: BOLA2, PSME2, MTAP, CA1, GSTA2, RALA, CNN2, CFL1, TCP1, HNRNPDL, MIF, AIP, SOD1, PPIA and PDCD4.

And the identified downregulated proteins are:

ANXA2, RPLP0, CAPZA1, SOD2, SNRPA1, LMNB1, LCP1, HSPA9, SERPINB2, HNRNPF, TALDO1, PAK2, TCP1, HNRNPA2B1, MSN, PITPNA, ARF1, SOD2, ANXA2, CDC42, RAP1B and GSTO1.

References

Rosengren AT, Nyman TA & Lahesmaa R (2005). Proteome profiling of interleukin-12 treated human T helper cells. Proteomics, 5, 3137-41.

Edit history

Date	Action	Author
2016-12-02	Authored	Duenas C
2016-12-02	Created	Duenas C
2017-05-11	Edited	Duenas C
2017-05-12	Reviewed	van de Vosse E

Date	Action	Author
2018-08-31	Modified	Orlic-Milacic M

Entities found in this pathway (8)

Input	UniProt Id
Anxa2	P07355
Hnrnpa2b1	P22626
Pitpna	Q00169

Input	UniProt Id
Capza1	P52907
Hnrnpf	P52597
Tcp1	P17987

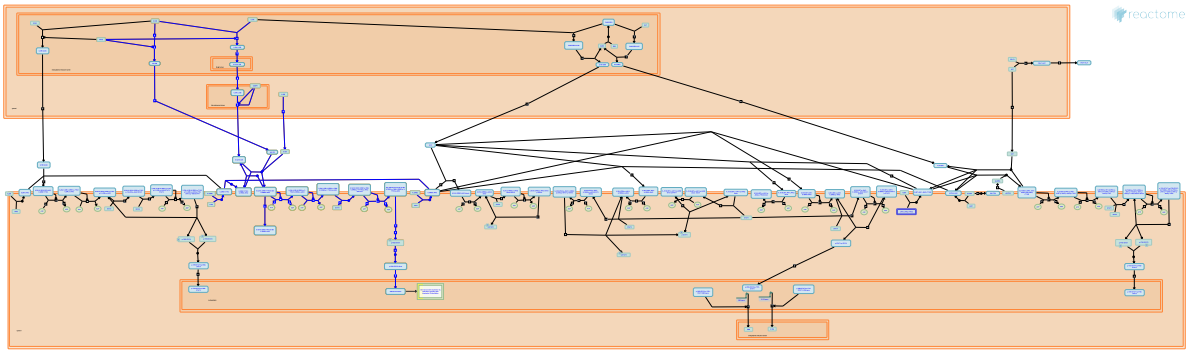
Input	UniProt Id
Cdc42	P60953
Hspa9	P38646

Input	Ensembl Id
Anxa2	ENSG00000182718
Hnrnpa2b1	ENSG00000122566
Pitpna	ENSG00000174238

Input	Ensembl Id
Capza1	ENSG00000116489
Hnrnpf	ENSG00000169813
Tcp1	ENSG00000120438

Input	Ensembl Id
Cdc42	ENSG00000070831
Hspa9	ENSG00000113013

3. Interleukin-12 signaling (R-HSA-9020591)



Interleukin 12 (IL-12) is heterodimeric cytokine produced by dendritic cells, macrophages and neutrophils. It is encoded by the genes Interleukin-12 subunit alpha (IL12A) and Interleukin-12 subunit beta (IL12B), which encode a 35-kDa light chain (p35) and a 40-kDa heavy chain (p40), respectively. The active IL12 heterodimer is sometimes referred to as p70. The p35 component has homology to single-chain cytokines, while p40 is homologous to the extracellular domains of members of the haematopoietic cytokine-receptor family. The IL12 heterodimer therefore resembles a cytokine linked to a soluble receptor.

IL12 is involved in the differentiation of naive T cells into Th1 cells and sometimes known as T cell-stimulating factor. IL12 enhances the cytotoxic activity of Natural Killer cells and CD8+ cytotoxic T lymphocytes. IL12 also has anti-angiogenic activity, mediated by increased production of CXCL10 via interferon gamma.

The IL12 receptor is a heterodimer formed by Interleukin-12 receptor subunit beta-1 (IL12RB1) and Interleukin-12 receptor subunit beta-2 (IL12RB2), both of which have extensive homology to IL6ST (gp130), the signal transducing receptor subunit of the IL6-like cytokine superfamily. IL-12RB2 is considered to play the key role in IL12 function, in part because its expression on activated T cells is stimulated by cytokines that promote Th1 cell development and inhibited by those that promote Th2 cells development. In addition, IL12 binding leads to IL12RB2 tyrosine phosphorylation, which provides binding sites for the kinases Non-receptor tyrosine-protein kinase TYK2 and Tyrosine-protein kinase JAK2. These activate transcription factor proteins in the Signal transducer and activator of transcription (STAT) family, particularly STAT4.

References

Watford WT, Moriguchi M, Morinobu A & O'Shea JJ (2003). The biology of IL-12: coordinating innate and adaptive immune responses. Cytokine Growth Factor Rev., 14, 361-8.

Edit history

Date	Action	Author
2014-06-04	Authored	Jupe S
2016-01-28	Reviewed	Meldal BH
2017-05-12	Reviewed	van de Vosse E
2017-05-17	Authored	Duenas C
2017-09-07	Created	Duenas C

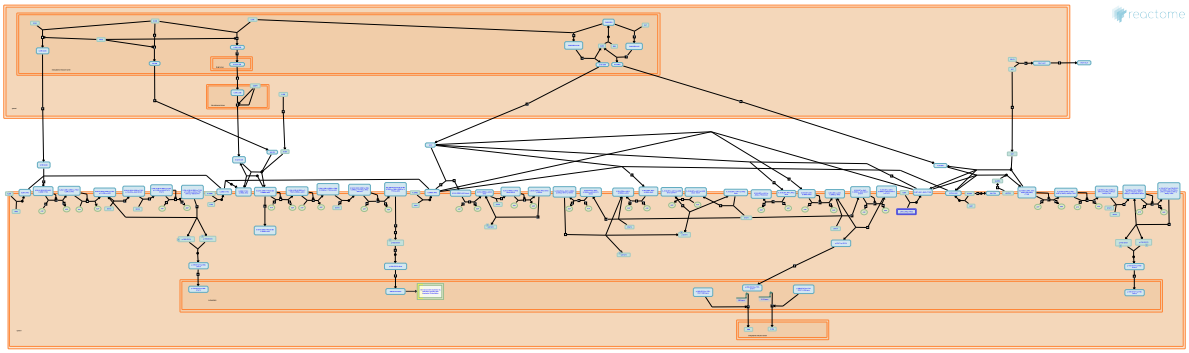
Date	Action	Author
2017-11-15	Edited	Jupe S
2021-09-10	Modified	Weiser JD

Entities found in this pathway (8)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Anxa2	P07355	Capza1	P52907	Cdc42	P60953
Hnrnpa2b1	P22626	Hnrnpf	P52597	Hspa9	P38646
Pitpna	Q00169	Tcp1	P17987		

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
Anxa2	ENSG00000182718	Capza1	ENSG00000116489	Cdc42	ENSG00000070831
Hnrnpa2b1	ENSG00000122566	Hnrnpf	ENSG00000169813	Hspa9	ENSG00000113013
Pitpna	ENSG00000174238	Tcp1	ENSG00000120438		

4. Interleukin-12 family signaling (R-HSA-447115)



Interleukin-12 (IL-12) is a heterodimer of interleukin-12 subunit alpha (IL12A, IL-12p35) and interleukin-12 subunit beta (IL12B, IL-12p40). It is a potent immunoregulatory cytokine involved in the generation of cell mediated immunity to intracellular pathogens. It is produced by antigen presenting cells, including dendritic cells, macrophages/monocytes, neutrophils and some B cells (D'Andrea et al. 1992, Kobayashi et al.1989, Heufler et al.1996). It enhances the cytotoxic activity of natural killer (NK) cells and cytotoxic T cells, stimulating proliferation of activated NK and T cells and induces production of interferon gamma (IFN gamma) by these cells (Stern et al. 1990). IL-12 also plays an important role in immunomodulation by promoting cell mediated immunity through induction of a class 1 T helper cell (Th1) immune response. IL-12 may contribute to immunopathological conditions such as rheumatoid arthritis (McIntyre et al. 1996).
The receptor for IL-12 is a heterodimer of IL-12Rbeta1 (IL12RB1) and IL-12Rbeta2 (IL12RB2), both highly homologous to Interleukin-6 receptor subunit beta (IL6ST,gp130). Each has an extracellular ligand binding domain, a transmembrane domain and a cytosolic domain containing box 1 and box 2 sequences that mediate binding of Janus family tyrosine kinases (JAKs). IL-12 binding is believed to bring about the heterodimerization and generation of a high affinity receptor complex capable of signal transduction. In this model, receptor dimerization leads to juxtaposition of the cytosolic domains and subsequent tyrosine phosphorylation and activation of JAK2 and TYK2. These activated kinases, in turn, tyrosine phosphorylate and activate several members of the signal transducer and activator of transcription (STAT) family, mainly STAT4, while also STAT1, STAT3 and STAT5 have been reported to be activated (Bacon et al. 1995, Jacobson et al. 1995, Yu et al. 1996, Gollob et al.1995). The STATs translocate to the nucleus to activate transcription of several genes, including IFN gamma. The production of IFN gamma has a pleiotropic effect in the cell, stimulating production of molecules important to cell mediated immunity. In particular, IFN gamma stimulates production of more IL-12 and sets up a positive regulation loop between IL-12 signaling and IFN gamma (Chan et al. 1991). The importance of IL-12 for this loop is demonstrated by IL-12 and STAT4 knockout mice that are severely compromised in IFN-gamma production (Kaplan et al. 1996; Magram et al. 1996), as well as by patients with IL12B mutations that are severely compromised in IFN-gamma production (Altare et al.1998).

References

D'Andrea A, Rengaraju M, Valiante NM, Chehimi J, Kubin M, Aste M, ... Nickbarg E (1992). Production of natural killer cell stimulatory factor (interleukin 12) by peripheral blood mononuclear cells. J Exp Med, 176, 1387-98.

Sun L, He C, Nair L, Yeung J & Egwuagu CE (2015). Interleukin 12 (IL-12) family cytokines: Role in immune pathogenesis and treatment of CNS autoimmune disease. Cytokine, 75, 249-55.

Behzadi P, Behzadi E & Ranjbar R (2016). IL-12 Family Cytokines: General Characteristics, Pathogenic Microorganisms, Receptors, and Signalling Pathways. Acta Microbiol Immunol Hung, 63, 1-25.

Edit history

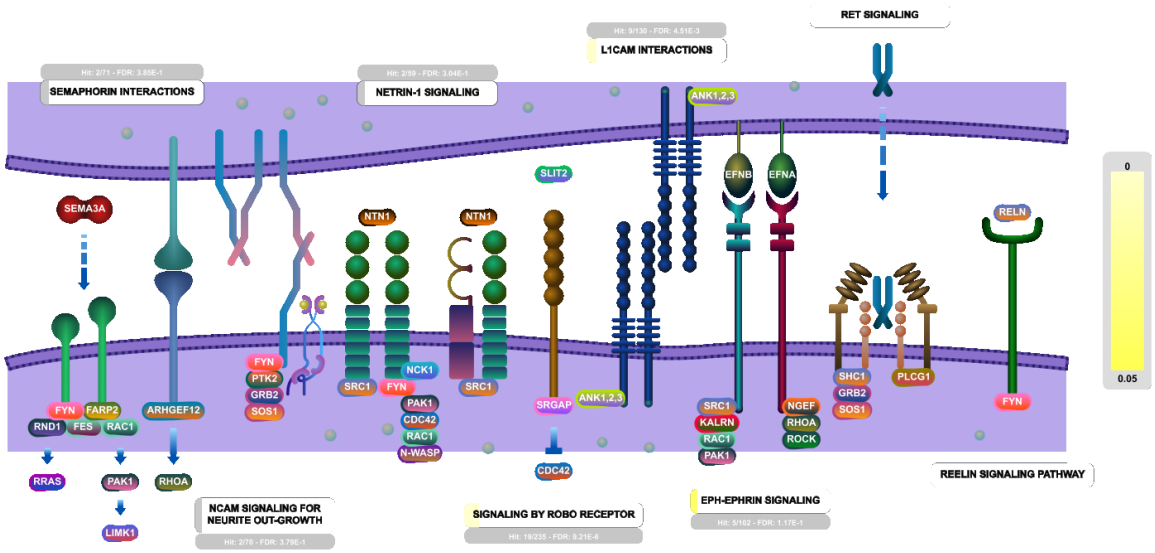
Date	Action	Author
2009-11-20	Created	Jupe S
2014-06-04	Authored	Jupe S
2016-01-28	Edited	Jupe S
2016-01-28	Reviewed	Meldal BH
2021-09-10	Modified	Weiser JD

Entities found in this pathway (8)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Anxa2	P07355	Capza1	P52907	Cdc42	P60953
Hnrnpa2b1	P22626	Hnrnpf	P52597	Hspa9	P38646
Pitpna	Q00169	Tcp1	P17987		

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
Anxa2	ENSG00000182718	Capza1	ENSG00000116489	Cdc42	ENSG00000070831
Hnrnpa2b1	ENSG00000122566	Hnrnpf	ENSG00000169813	Hspa9	ENSG00000113013
Pitpna	ENSG00000174238	Tcp1	ENSG00000120438		

5. Axon guidance (R-HSA-422475)



Axon guidance / axon pathfinding is the process by which neurons send out axons to reach the correct targets. Growing axons have a highly motile structure at the growing tip called the growth cone, which senses the guidance cues in the environment through guidance cue receptors and responds by undergoing cytoskeletal changes that determine the direction of axon growth.

Guidance cues present in the surrounding environment provide the necessary directional information for the trip. These extrinsic cues have been divided into attractive or repulsive signals that tell the growth cone where and where not to grow.

Genetic and biochemical studies have led to the identification of highly conserved families of guidance molecules and their receptors that guide axons. These include netrins, Slits, semaphorins, and ephrins, and their cognate receptors, DCC and or uncoordinated-5 (UNC5), roundabouts (Robo), neuropilin and Eph. In addition, many other classes of adhesion molecules are also used by growth cones to navigate properly which include NCAM and L1CAM.

For review of axon guidance, please refer to Russel and Bashaw 2018, Chedotal 2019, Suter and Jaworski 2019).

Axon guidance cues and their receptors are implicated in cancer progression (Biankin et al. 2012), where they likely contribute to cell migration and angiogenesis (reviewed by Mehlen et al. 2011).

References

Chédotal A (2019). Roles of axon guidance molecules in neuronal wiring in the developing spinal cord. Nat. Rev. Neurosci., 20, 380-396.

Suter TACS & Jaworski A (2019). Cell migration and axon guidance at the border between central and peripheral nervous system. Science, 365.

Russell SA & Bashaw GJ (2018). Axon guidance pathways and the control of gene expression. Dev. Dyn., 247, 571-580.

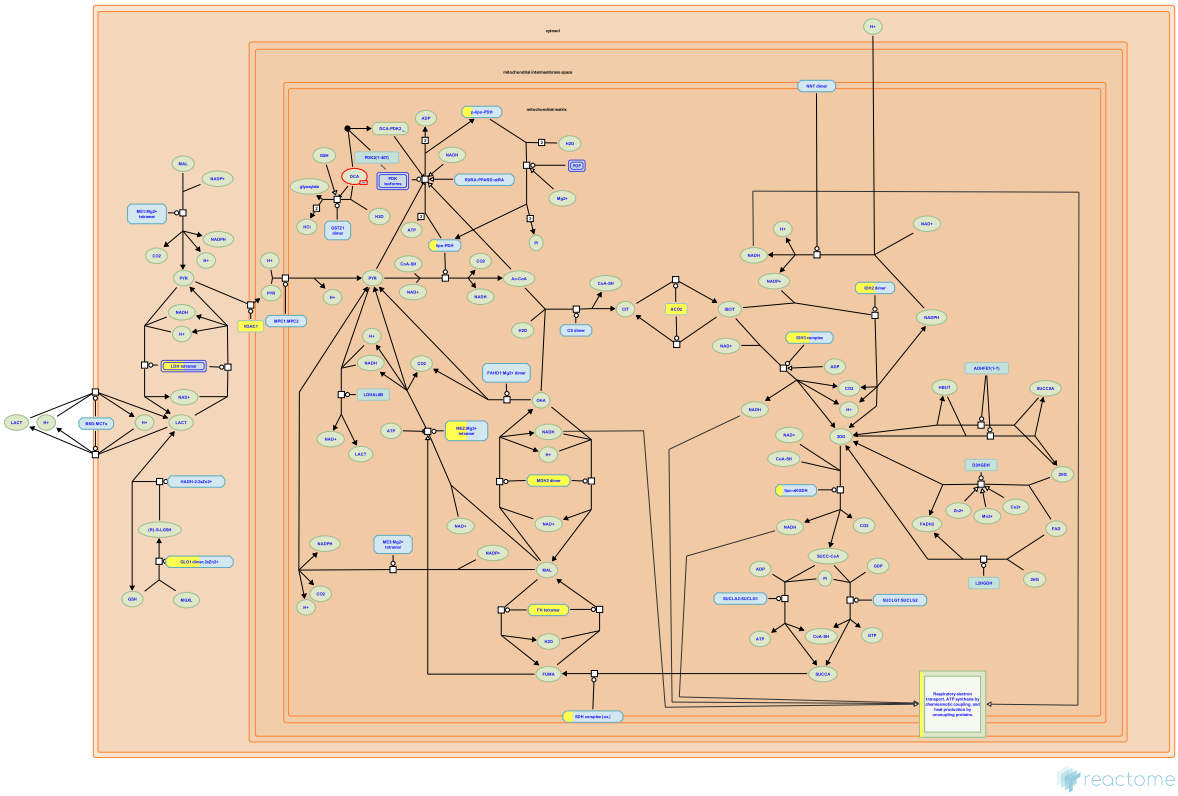
Edit history

Date	Action	Author
2009-05-26	Reviewed	Walmod PS, Maness PF
2009-05-28	Edited	Garapati P V
2009-05-28	Authored	Garapati P V
2009-05-31	Created	Garapati P V
2021-09-10	Modified	Weiser JD

Entities found in this pathway (32)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Actr3	P61158	Ap2b1	P63010	Cap1	Q01518
Cdc42	P60953	Col6a5	A8TX70	Csnk2b	P67870
Hspa8	P11142	Lamb1	P07942	Lypla2	O95372
Myl12b	O14950	Pfn1	P07737	Pitpna	Q00169
Psma2	P25787	Psma4	P25789	Psma6	P60900
Psmb10	P40306	Psmb3	P49720	Psmb4	P28070
Psmc3	P17980	RPS13	P62277	RPS3A	P61247
Rlc-a	P19105	Rpl18	Q07020	Rpl30	P62888
Rpl4	P36578	Rplp1	P05386	Rps5	P46782
Rps7	P62081	Rps9	P46781	Sptbn1	Q01082
Tln1	Q9Y490	Tubb4b	P04350, P68371, Q3ZCM7		

6. The citric acid (TCA) cycle and respiratory electron transport (R-HSA-1428517)



The metabolism of pyruvate provides one source of acetyl-CoA which enters the citric acid (TCA, tricarboxylic acid) cycle to generate energy and the reducing equivalent NADH. These reducing equivalents are re-oxidized back to NAD+ in the electron transport chain (ETC), coupling this process with the export of protons across the inner mitochondrial membrane. The chemiosmotic gradient created is used to drive ATP synthesis.

References

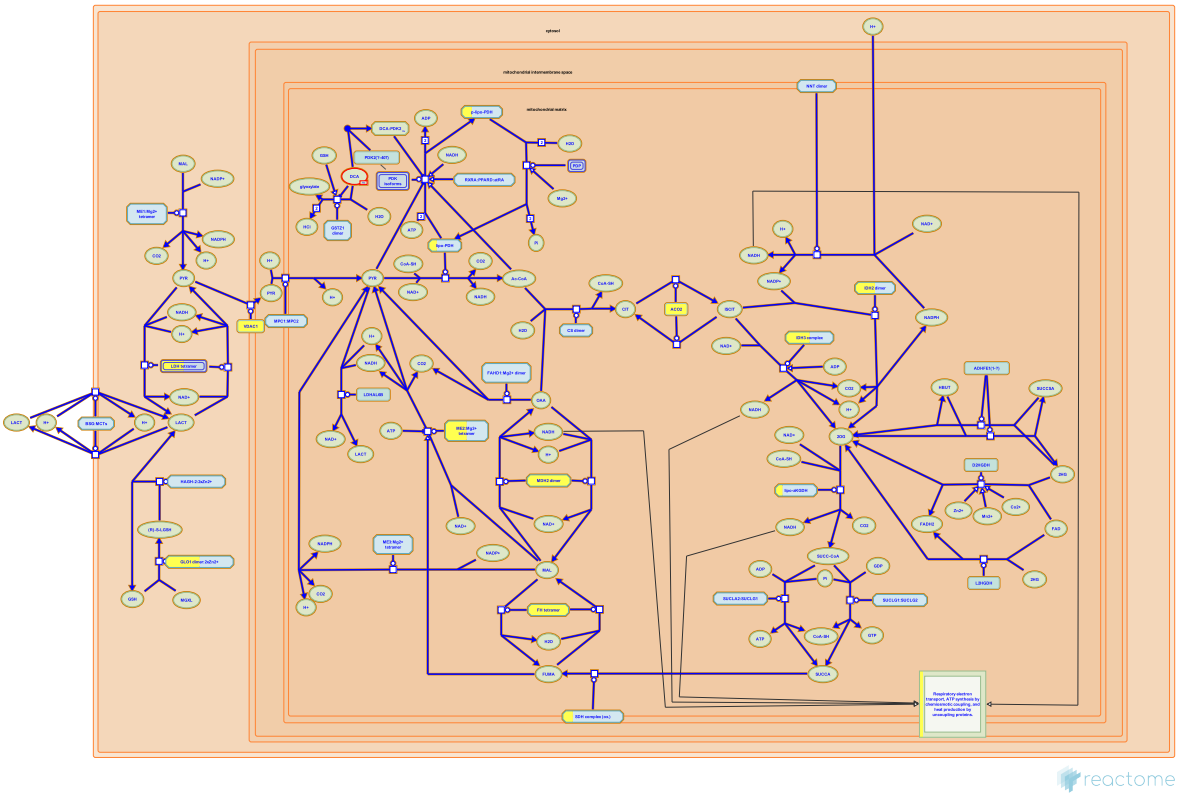
Edit history

Date	Action	Author
2003-11-03	Authored	Birney E, Schmidt EE, D'Eustachio P
2011-07-07	Edited	Jassal B
2011-07-07	Created	Jassal B
2021-09-10	Modified	Weiser JD

Entities found in this pathway (21)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Aco1	Q99798	Dlat	P10515	Dld	P09622
Etfa	P13804	Fh	P07954	Glo1	Q04760
Idh1	P51553	Idh2	P48735, P50213	Idh3g	P51553
Ldha	P00338	Ldhb	P07195	Mdh1	P40926
Me2	P23368	Mtco2	P00403	Ndufab1	O14561
Ndufs2	O75306	Ndufv2	P19404	Sdhb	P21912
Uqcr10	Q9UDW1	Uqcrh	P07919	Vdac1	P21796

7. Pyruvate metabolism and Citric Acid (TCA) cycle (R-HSA-71406)



Pyruvate metabolism and the citric acid (TCA) cycle together link the processes of energy metabolism in a human cell with one another and with key biosynthetic reactions. Pyruvate, derived from the reversible oxidation of lactate or transamination of alanine, can be converted to acetyl CoA. Other sources of acetyl CoA include breakdown of free fatty acids and ketone bodies in the fasting state. Acetyl CoA can enter the citric acid cycle, a major source of reducing equivalents used to synthesize ATP, or enter biosynthetic pathways.

In addition to its role in energy generation, the citric acid cycle is a source of carbon skeletons for amino acid metabolism and other biosynthetic processes. One such process included here is the interconversion of 2-hydroxyglutarate, probably derived from porphyrin and amino acid metabolism, and 2-oxoglutarate (alpha-ketoglutarate), a citric acid cycle intermediate.

References

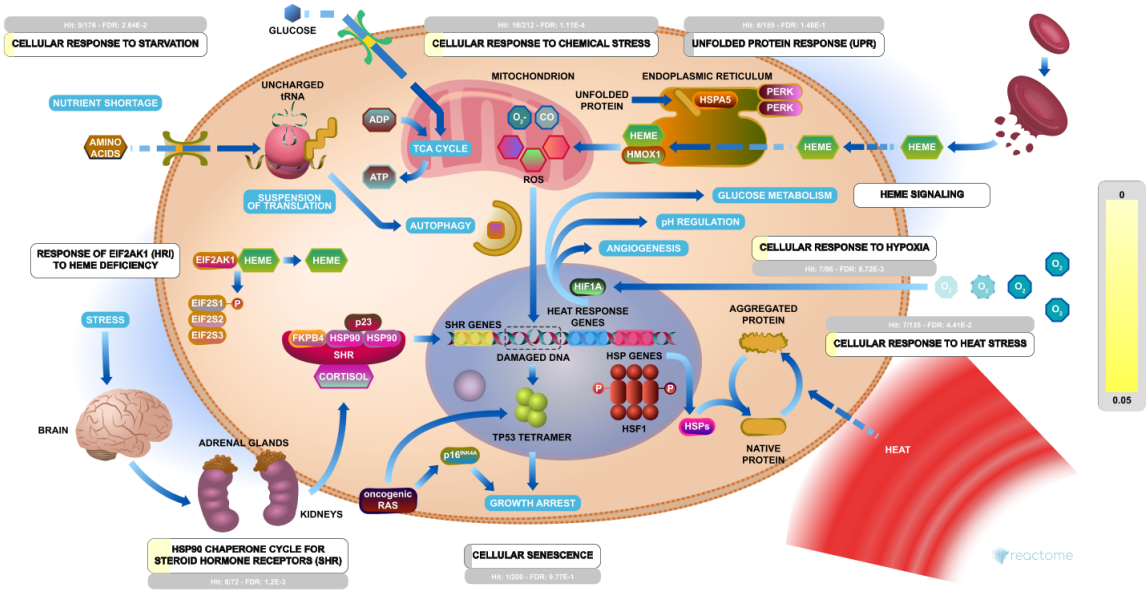
Edit history

Date	Action	Author
2003-11-03	Authored	Birney E, Schmidt EE, D'Eustachio P
2003-11-03	Created	Birney E, Schmidt EE, D'Eustachio P
2010-01-17	Revised	D'Eustachio P
2021-08-26	Edited	D'Eustachio P
2021-09-10	Modified	Weiser JD

Entities found in this pathway (14)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Aco1	Q99798	Dlat	P10515	Dld	P09622
Fh	P07954	Glo1	Q04760	Idh1	P51553
Idh2	P48735, P50213	Idh3g	P51553	Ldha	P00338
Ldhb	P07195	Mdh1	P40926	Me2	P23368
Sdhb	P21912	Vdac1	P21796		

8. Cellular responses to stress (R-HSA-2262752)



Cells are subject to external molecular and physical stresses such as foreign molecules that perturb metabolic or signaling processes, and changes in temperature or pH. Cells are also subject to internal molecular stresses such as production of reactive metabolic byproducts. The ability of cells and tissues to modulate molecular processes in response to such stresses is essential to the maintenance of tissue homeostasis (Kultz 2005). Specific stress-related processes annotated here are **cellular response to hypoxia**, **cellular response to heat stress**, **cellular senescence**, **HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand**, **response of EIF2AK1 (HRI) to heme deficiency**, **heme signaling**, **cellular response to chemical stress**, **cellular response to starvation**, and **unfolded protein response**.

References

Kültz D (2005). Molecular and evolutionary basis of the cellular stress response. Annu. Rev. Physiol. , 67, 225-57.

Edit history

Date	Action	Author
2012-05-20	Edited	Matthews L
2012-05-20	Reviewed	D'Eustachio P
2012-05-20	Authored	Matthews L
2012-05-20	Created	Matthews L
2021-09-10	Modified	Weiser JD

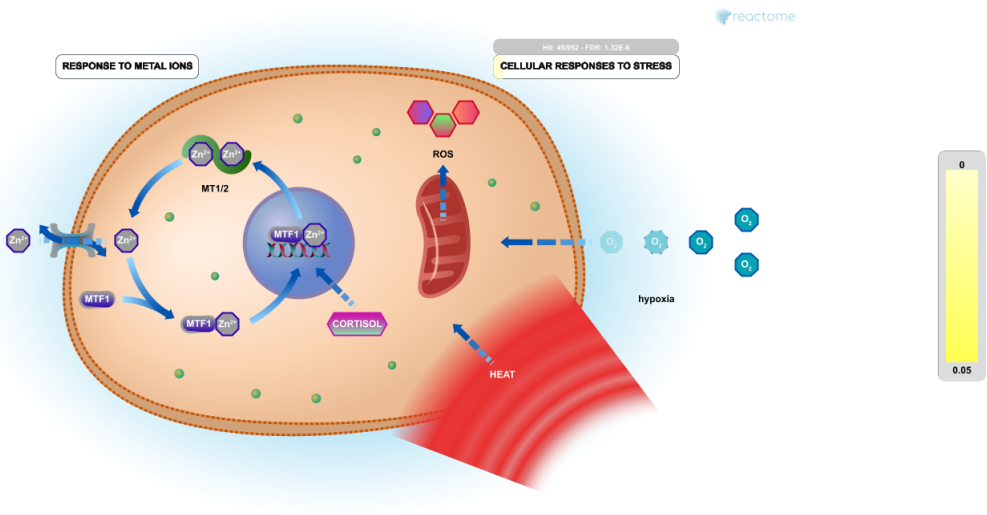
Entities found in this pathway (38)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Acadvl	P49748	Cap1	P47755	Capza1	P52907
Capza2	P47755	Cdh1	Q9UM11	Csnk2b	P67870
Dync1h1	Q14204	Eef1a1	P68104	Gpx3	O75715, P22352

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Gsr	P00390-1, P00390-2	Hspa2	P54652	Hspa4	P34932
Hspa8	P11142	Hspa9	P38646	Mtco2	P00403
Pdia6	Q15084	Prdx2	P32119	Prdx5	P30044-1, P30044-2
Psma2	P25787	Psma4	P25789	Psma6	P60900
Psmb10	P40306	Psmb3	P49720	Psmb4	P28070
Psmc3	P17980	RPS13	P62277	RPS3A	P61247
Rpl18	Q07020	Rpl30	P62888	Rpl4	P36578
Rplp1	P05386	Rps5	P46782	Rps7	P62081
Rps9	P46781	St13	P50502	Tln1	Q9Y490
Tubb4b	P04350, P68371, Q3ZCM7	Ywhae	P62258		

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
Acadvl	ENSG00000072778	Pdia6	ENSG00000143870	Tln1	ENSG00000137076

9. Cellular responses to stimuli (R-HSA-8953897)



Individual cells detect and respond to diverse external molecular and physical signals. Appropriate responses to these signals are essential for normal development, maintenance of homeostasis in mature tissues, and effective defensive responses to potentially noxious agents (Kultz 2005). It is convenient, if somewhat arbitrary, to distinguish responses to signals involved in development and homeostasis from ones involved in stress responses, and that classification is followed here, with **macroautophagy** and **responses to metal ions** classified as responses to normal external stimuli, while responses to hypoxia, reactive oxygen species, and heat, and the process of cellular senescence are classified as **stress responses**. Signaling cascades are integral components of all of these response mechanisms but because of their number and diversity, they are grouped in a separate signal transduction superpathway in Reactome.

References

Kültz D (2005). Molecular and evolutionary basis of the cellular stress response. Annu. Rev. Physiol. , 67, 225-57.

Edit history

Date	Action	Author
2012-05-20	Reviewed	D'Eustachio P
2015-05-13	Reviewed	Tooze SA
2015-09-03	Reviewed	Klionsky DJ
2015-09-19	Reviewed	Atrian S
2016-12-30	Edited	D'Eustachio P
2016-12-30	Authored	D'Eustachio P
2016-12-30	Created	D'Eustachio P
2021-09-10	Modified	Weiser JD

Entities found in this pathway (38)

Input	UniProt Id
Acadvl	P49748
Capza2	P47755
Dync1h1	Q14204
Gsr	P00390-1, P00390-2
Hspa8	P11142
Pdia6	Q15084
Psma2	P25787
Psmb10	P40306
Psmc3	P17980
Rpl18	Q07020
Rplp1	P05386
Rps9	P46781
Tubb4b	P04350, P68371, Q3ZCM7

Input	UniProt Id
Cap1	P47755
Cdh1	Q9UM11
Eef1a1	P68104
Hspa2	P54652
Hspa9	P38646
Prdx2	P32119
Psma4	P25789
Psmb3	P49720
RPS13	P62277
Rpl30	P62888
Rps5	P46782
St13	P50502
Ywhae	P62258

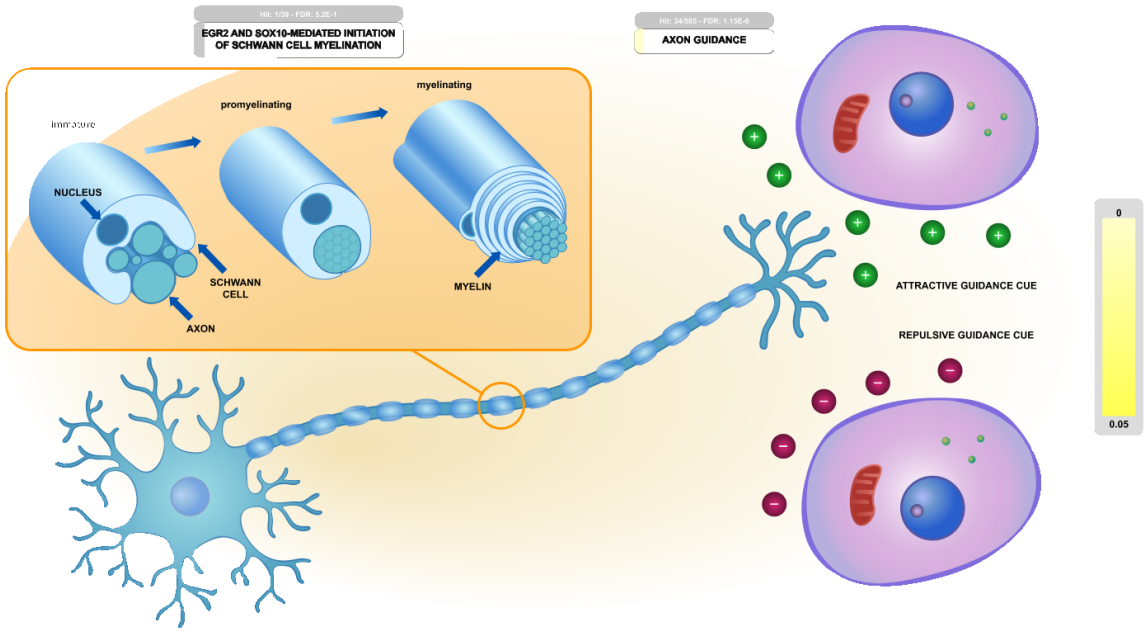
Input	UniProt Id
Capza1	P52907
Csnk2b	P67870
Gpx3	O75715, P22352
Hspa4	P34932
Mtco2	P00403
Prdx5	P30044-1, P30044-2
Psma6	P60900
Psmb4	P28070
RPS3A	P61247
Rpl4	P36578
Rps7	P62081
Tln1	Q9Y490

Input	Ensembl Id
Acadvl	ENSG00000072778

Input	Ensembl Id
Pdia6	ENSG00000143870

Input	Ensembl Id
Tln1	ENSG00000137076

10. Nervous system development (R-HSA-9675108)



Neurogenesis is the process by which neural stem cells give rise to neurons, and occurs both during embryonic and perinatal development as well as in specific brain lineages during adult life (reviewed in Gotz and Huttner, 2005; Yao et al, 2016; Kriegstein and Alvarez-Buylla, 2009).

References

Götz M & Huttner WB (2005). The cell biology of neurogenesis. Nat. Rev. Mol. Cell Biol., 6, 777-88.

Yao B, Christian KM, He C, Jin P, Ming GL & Song H (2016). Epigenetic mechanisms in neurogenesis. Nat. Rev. Neurosci., 17, 537-49.

Kriegstein A & Alvarez-Buylla A (2009). The glial nature of embryonic and adult neural stem cells. Annu. Rev. Neurosci., 32, 149-84.

Edit history

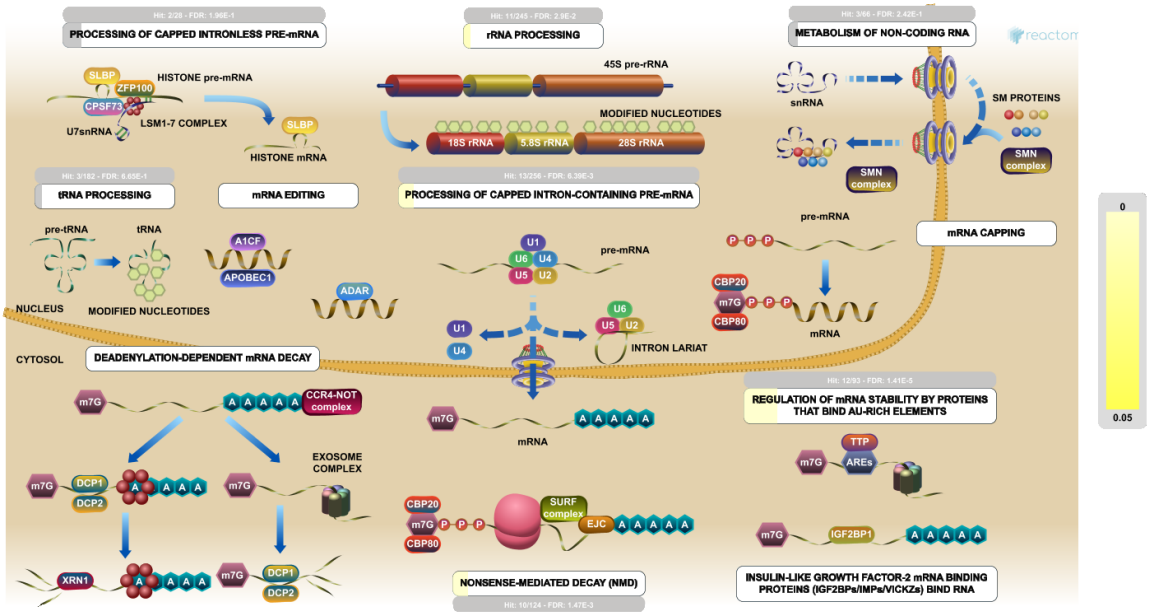
Date	Action	Author
2020-01-23	Reviewed	Orlic-Milacic M
2020-01-31	Edited	Rothfels K
2020-01-31	Authored	Rothfels K
2020-01-31	Created	Rothfels K
2021-09-10	Modified	Weiser JD

Entities found in this pathway (32)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Actr3	P61158	Ap2b1	P63010	Cap1	Q01518
Cdc42	P60953	Col6a5	A8TX70	Csnk2b	P67870
Hspa8	P11142	Lamb1	P07942	Lypla2	O95372
Myl12b	O14950	Pfn1	P07737	Pitpna	Q00169

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Psma2	P25787	Psma4	P25789	Psma6	P60900
Psmb10	P40306	Psmb3	P49720	Psmb4	P28070
Psmc3	P17980	RPS13	P62277	RPS3A	P61247
Rlc-a	P19105	Rpl18	Q07020	Rpl30	P62888
Rpl4	P36578	Rplp1	P05386	Rps5	P46782
Rps7	P62081	Rps9	P46781	Sptbn1	Q01082
Tln1	Q9Y490	Tubb4b	P04350, P68371, Q3ZCM7		

11. Metabolism of RNA (R-HSA-8953854)



This superpathway encompasses the processes by which RNA transcription products are further modified covalently and non-covalently to yield their mature forms, and the regulation of these processes. Annotated pathways include ones for capping, splicing, and 3'-cleavage and poly-adenylation to yield mature mRNA molecules that are exported from the nucleus (Hocine et al. 2010). mRNA editing and nonsense-mediated decay are also annotated. Processes leading to mRNA breakdown are described: deadenylation-dependent mRNA decay, microRNA-mediated RNA cleavage, and regulation of mRNA stability by proteins that bind AU-rich elements.psnRNP assembly is also annotated here.

The aminoacylation of mature tRNAs is annotated in the "Metabolism of proteins" superpathway, as a part of "Translation".

References

Hocine S, Singer RH & Grünwald D (2010). RNA processing and export. Cold Spring Harb Perspect Biol, 2, a000752.

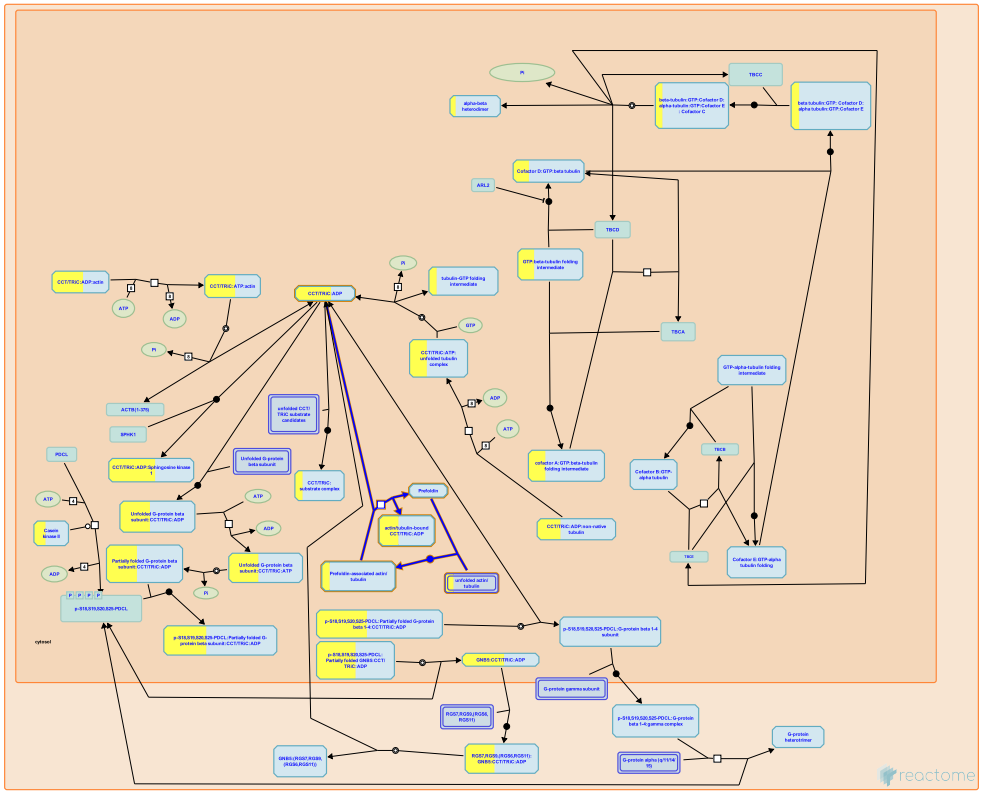
Edit history

Date	Action	Author
2016-12-29	Edited	D'Eustachio P
2016-12-29	Authored	D'Eustachio P
2016-12-29	Created	D'Eustachio P
2016-12-30	Revised	D'Eustachio P
2017-02-28	Reviewed	Gillespie ME
2021-09-10	Modified	Weiser JD

Entities found in this pathway (36)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Anp32a	P39687	Ddx39b	Q13838	Dhx15	O43143
Dhx9	Q08211	Eprs	P07814	Hnrnpa2b1	P22626
Hnrnpc	P07910	Hnrnpd	Q14103, Q14103-3, Q14103-4	Hnrnpf	P52597
Hnrnph2	P55795	Hsd17b10	Q99714	Hspa8	P11142
Ncl	P19338	Ppp2r1a	P30153	Psma2	P25787
Psma4	P25789	Psma6	P60900	Psmb10	P40306
Psmb3	P49720	Psmb4	P28070	Psmc3	P17980
Ptbp1	P26599	RPS13	P62277	RPS3A	P61247
Rpl18	Q07020	Rpl30	P62888	Rpl4	P36578
Rplp1	P05386	Rps5	P46782	Rps7	P62081
Rps9	P46781	Rtcb	Q9Y3I0	SNRPE	P62304
Snrpd2	P62316	Snrpd3	P62318	Ywhaz	P63104

12. Prefoldin mediated transfer of substrate to CCT/TriC (R-HSA-389957)



Cellular compartments: cytosol.

Unfolded actins and tubulins bound to prefoldin are transferred to CCT via a docking mechanism (McCormack and Willison, 2001).

References

McCormack EA, Llorca O, Carrascosa JL, Valpuesta JM & Willison KR (2001). Point mutations in a hinge linking the small and large domains of beta-actin result in trapped folding intermediates bound to cytosolic chaperonin CCT. J Struct Biol, 135, 198-204.

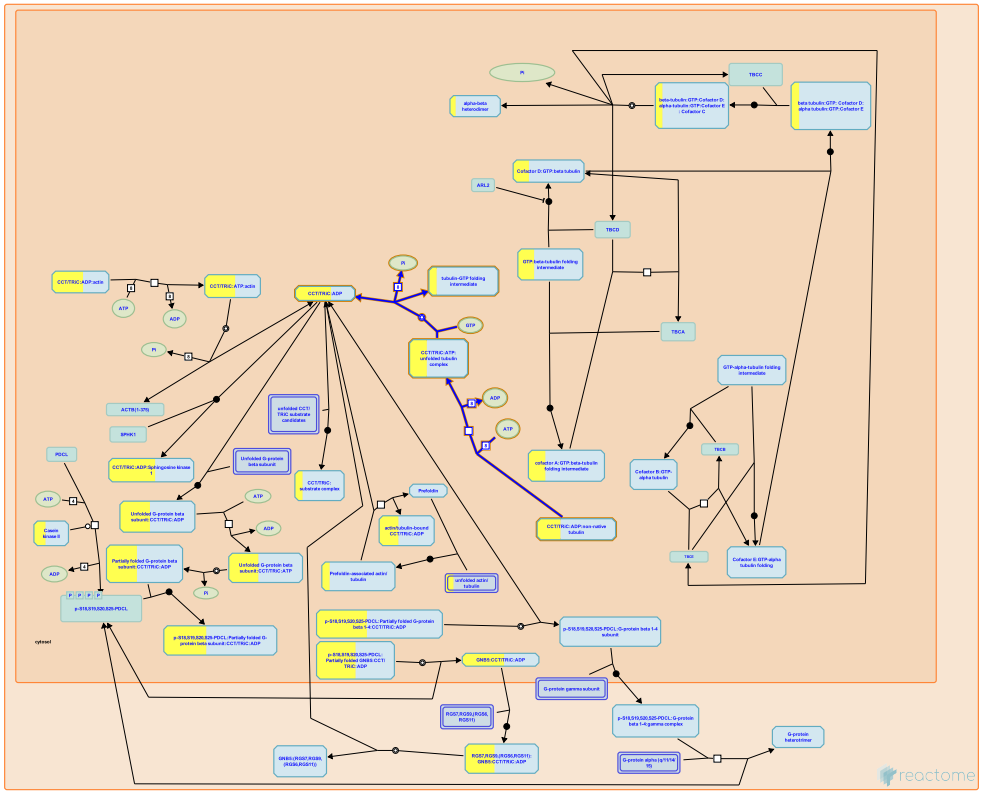
Edit history

Date	Action	Author
2008-12-01	Authored	Matthews L
2009-01-21	Reviewed	Cowan NJ
2009-01-22	Created	Matthews L
2009-02-21	Edited	Matthews L
2017-05-16	Modified	Matthews L

Entities found in this pathway (7)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Cct2	P78371	Cct3	P49368	Cct4	P50991
Cct7	Q99832	Cct8	P50990	Tcp1	P17987
Tubb4b	P04350, P68371				

13. Formation of tubulin folding intermediates by CCT/TriC (R-HSA-389960)



Cellular compartments: cytosol.

TriC/CCT forms a binary complex with unfolded alpha- or beta-tubulin (Frydman et al., 1992; Gao et al., 1993). The tubulin folding intermediates produced by TriC are unstable (Gao et al., 1993). Five additional protein cofactors (cofactor A-E) are required for the generation of properly folded alpha- and beta-tubulin and for the formation of alpha/beta-tubulin heterodimers (Gao et al., 1993) (Tian et al., 1997, Cowan and Lewis 2001).

References

Frydman J, Nimmesgern E, Erdjument-Bromage H, Wall JS, Tempst P & Hartl FU (1992). Function in protein folding of TRiC, a cytosolic ring complex containing TCP-1 and structurally related subunits. EMBO J, 11, 4767-78.

Tian G, Lewis SA, Feierbach B, Stearns T, Rommelaere H, Ampe C & Cowan NJ (1997). Tubulin subunits exist in an activated conformational state generated and maintained by protein cofactors. J Cell Biol, 138, 821-32.

Gao Y, Vainberg IE, Chow RL & Cowan NJ (1993). Two cofactors and cytoplasmic chaperonin are required for the folding of alpha- and beta-tubulin. Mol Cell Biol, 13, 2478-85.

Cowan NJ & Lewis SA (2001). Type II chaperonins, prefoldin, and the tubulin-specific chaperones. Adv Protein Chem, 59, 73-104.

Edit history

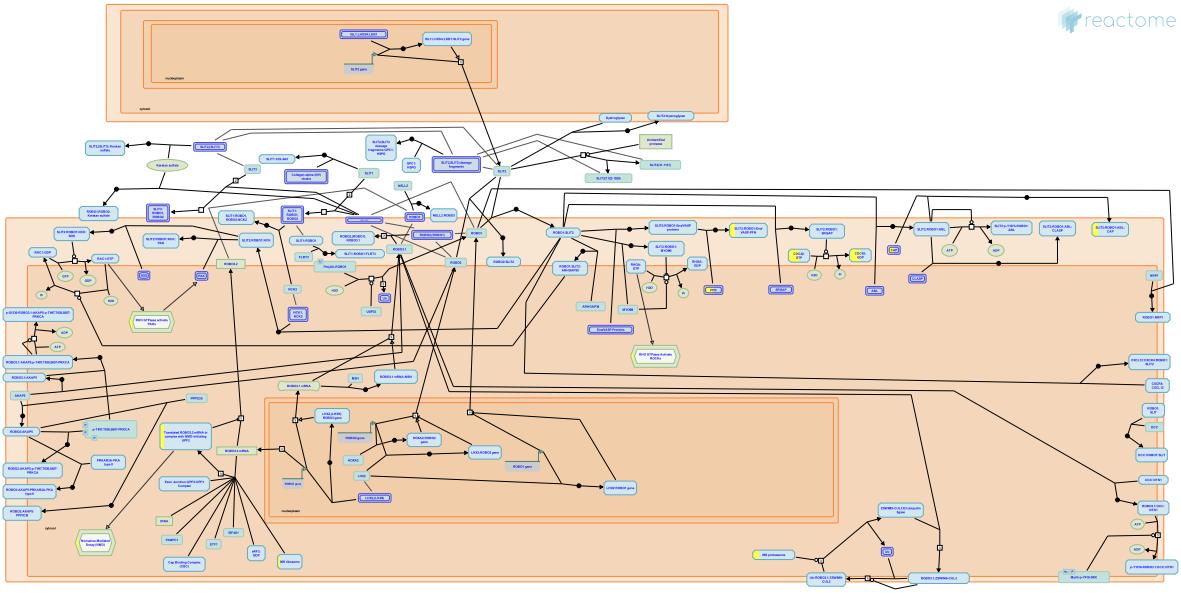
Date	Action	Author
2008-12-01	Authored	Matthews L
2009-01-21	Reviewed	Cowan NJ

Date	Action	Author
2009-01-22	Created	Matthews L
2009-02-21	Edited	Matthews L
2017-05-16	Modified	Matthews L

Entities found in this pathway (7)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Cct2	P78371	Cct3	P49368	Cct4	P50991
Cct7	Q99832	Cct8	P50990	Tcp1	P17987
Tubb4b	P04350, P68371				

14. Signaling by ROBO receptors (R-HSA-376176)



Cellular compartments: plasma membrane.

The Roundabout (ROBO) family encodes transmembrane receptors that regulate axonal guidance and cell migration. The major function of the Robo receptors is to mediate repulsion of the navigating growth cones. There are four human Robo homologues, ROBO1, ROBO2, ROBO3 and ROBO4. Most of the ROBOs have the similar ectodomain architecture as the cell adhesion molecules, with five Ig domains followed by three FN3 repeats, except for ROBO4. ROBO4 has two Ig and two FN3 repeats. The cytoplasmic domains of ROBO receptors are in general poorly conserved. However, there are four short conserved cytoplasmic sequence motifs, named CC0-3, that serve as binding sites for adaptor proteins. The ligands for the human ROBO1 and ROBO2 receptors are the three SLIT proteins SLIT1, SLIT2, and SLIT3; all of the SLIT proteins contain a tandem of four LRR (leucine rich repeat) domains at the N-terminus, termed D1-D4, followed by six EGF (epidermal growth factor)-like domains, a laminin G like domain (ALPS), three EGF-like domains, and a C-terminal cysteine knot domain. Most SLIT proteins are cleaved within the EGF-like region by unknown proteases (reviewed by Hohenster 2008, Ypsilanti and Chedotal 2014, Blockus and Chedotal 2016). NELL2 is a ligand for ROBO3 (Jaworski et al. 2015).

SLIT protein binding modulates ROBO interactions with the cytosolic adaptors. The cytoplasmic domain of ROBO1 and ROBO2 determines the repulsive responses of these receptors. Based on the studies from both invertebrate and vertebrate organisms it has been inferred that ROBO induces growth cone repulsion by controlling cytoskeletal dynamics via either Abelson kinase (ABL) and Enabled (Ena), or RAC1 activity (reviewed by Hohenster 2008, Ypsilanti and Chedotal 2014, Blockus and Chedotal 2016). While there is some redundancy in the function of ROBO receptors, ROBO1 is implicated as the predominant receptor for axon guidance in ventral tracts, and ROBO2 is the predominant receptor for axon guidance in dorsal tracts. ROBO2 also repels neuron cell bodies from the floor plate (Kim et al. 2011).

In addition to regulating axon guidance, ROBO1 and ROBO2 receptors are also implicated in regulation of proliferation and transition of primary to intermediate neuronal progenitors through a poorly characterized cross-talk with NOTCH-mediated activation of HES1 transcription (Borrell et al. 2012).

Thalamocortical axon extension is regulated by neuronal activity-dependent transcriptional regulation of ROBO1 transcription. Lower neuronal activity correlates with increased ROBO1 transcription, possibly mediated by the NFKB complex (Mire et al. 2012).

It is suggested that the homeodomain transcription factor NKX2.9 stimulates transcription of ROBO2, which is involved in regulation of motor axon exit from the vertebrate spinal code (Bravo-Ambrosio et al. 2012).

Of the four ROBO proteins, ROBO4 is not involved in neuronal system development but is, instead, involved in angiogenesis. The interaction of ROBO4 with SLIT3 is involved in proliferation, motility and chemotaxis of endothelial cells, and accelerates formation of blood vessels (Zhang et al. 2009).

References

Hohenester E (2008). Structural insight into Slit-Robo signalling. Biochem Soc Trans, 36, 251-6.

Borrell V, Cárdenas A, Ciceri G, Galcerán J, Flames N, Pla R, ... Marín O (2012). Slit/Robo signaling modulates the proliferation of central nervous system progenitors. Neuron, 76, 338-52.

Mire E, Mezzera C, Leyva-Díaz E, Paternain AV, Squarzoni P, Bluy L, ... López-Bendito G (2012). Spontaneous activity regulates Robo1 transcription to mediate a switch in thalamocortical axon growth. Nat. Neurosci., 15, 1134-43.

Bravo-Ambrosio A, Mastick G & Kaprielian Z (2012). Motor axon exit from the mammalian spinal cord is controlled by the homeodomain protein Nkx2.9 via Robo-Slit signaling. Development, 139, 1435-46.

Zhang B, Dietrich UM, Geng JG, Bicknell R, Esko JD & Wang L (2009). Repulsive axon guidance molecule Slit3 is a novel angiogenic factor. Blood, 114, 4300-9.

Edit history

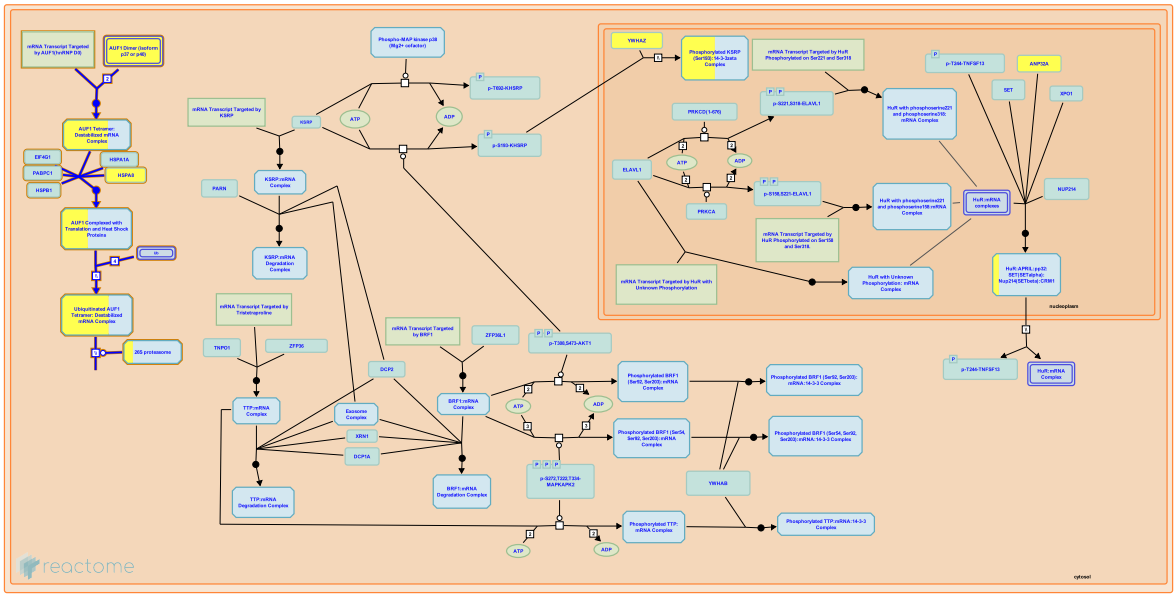
Date	Action	Author
2008-09-05	Edited	Garapati P V
2008-09-05	Authored	Garapati P V
2008-09-05	Created	Garapati P V
2009-08-18	Reviewed	Kidd T
2017-06-23	Revised	Orlic-Milacic M
2017-06-23	Edited	Orlic-Milacic M
2017-07-31	Reviewed	Jaworski A
2017-08-04	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

Entities found in this pathway (19)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Cap1	Q01518	Cdc42	P60953	Pfn1	P07737
Psma2	P25787	Psma4	P25789	Psma6	P60900
Psmb10	P40306	Psmb3	P49720	Psmb4	P28070
Psmc3	P17980	RPS13	P62277	RPS3A	P61247

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Rpl18	Q07020	Rpl30	P62888	Rpl4	P36578
Rplp1	P05386	Rps5	P46782	Rps7	P62081
Rps9	P46781				

15. AUF1 (hnRNP D0) binds and destabilizes mRNA (R-HSA-450408)



Cellular compartments: cytosol.

AUF1 (hnRNP D0) dimers bind U-rich regions of AU-rich elements (AREs) in the 3' untranslated regions of mRNAs. The binding causes AUF1 dimers to assemble into higher order tetrameric complexes. Diphosphorylated AUF1 bound to RNA recruits additional proteins, including eIF4G, polyA-binding protein, Hsp, Hsc70, Hsp27, NSEP-1, NSAP-1, and IMP-2 which target the mRNA and AUF1 for degradation. Unphosphorylated AUF1 is thought to be less able to recruit additional proteins. AUF1 also interacts directly or indirectly with HuR and the RNA-induced silencing complex (RISC).

AUF1 complexed with RNA and other proteins is ubiquitinated and targeted for destruction by the proteasome while the bound mRNA is degraded. Inhibition of ubiquitin addition to AUF1 blocks mRNA degradation. The mechanism by which ubiquitin-dependent proteolysis is coupled to mRNA degradation is unknown.

At least 4 isoforms of AUF1 exist: p45 (45 kDa) contains all exons, p42 lacks exon 2, p40 lacks exon 7, and p37 lacks exons 2 and 7. The presence of exon 7 in p42 and p45 seems to block ubiquitination while the absence of exon 7 (p37 and p40) targets AUF1 for ubiquitination and destabilizes bound RNAs. Lack of exon 2 (p37 and p42) is associated with higher affinity for RNA and 14-3-3sigma (SFN).

AUF1 binds and destabilizes mRNAs encoding Interleukin-1 beta (IL1B), Tumor Necrosis Factor alpha (TNFA), Cyclin-dependent kinase inhibitor 1 (CDNK1A, p21), Cyclin-D1 (CCND1), Granulocyte-macrophage colony stimulating factor (GM-CSF, CSF2), inducible Nitric oxide synthase (iNOS, NOS2), Proto-oncogene cFos (FOS), Myc proto-oncogene (MYC), Apoptosis regulator Bcl-2 (BCL2).

References

Sinsimer KS, Gratacos FM, Knapinska AM, Lu J, Krause CD, Wierzbowski AV, ... Brewer G (2008). Chaperone Hsp27, a novel subunit of AUF1 protein complexes, functions in AU-rich element-mediated mRNA decay. Mol Cell Biol, 28, 5223-37.

Wilson GM, Lu J, Sutphen K, Sun Y, Huynh Y & Brewer G (2003). Regulation of A + U-rich element-directed mRNA turnover involving reversible phosphorylation of AUF1. J Biol Chem, 278, 33029-38.

Laroia G, Cuesta R, Brewer G & Schneider RJ (1999). Control of mRNA decay by heat shock-ubiquitin-proteasome pathway. Science, 284, 499-502.

Zhang T, Kruys V, Huez G & Gueydan C (2002). AU-rich element-mediated translational control: complexity and multiple activities of trans-activating factors. Biochem Soc Trans, 30, 952-8.

Barreau C, Paillard L & Osborne HB (2005). AU-rich elements and associated factors: are there unifying principles?. Nucleic Acids Res, 33, 7138-50.

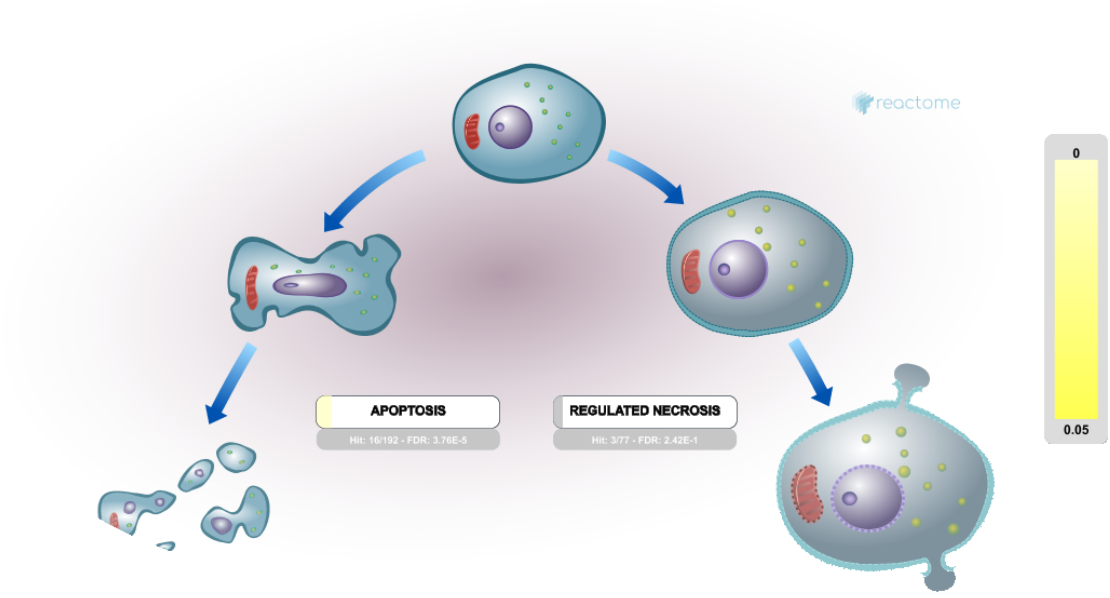
Edit history

Date	Action	Author
2009-12-17	Created	May B
2009-12-29	Edited	May B
2009-12-29	Authored	May B
2010-06-29	Reviewed	Wilusz J
2021-09-10	Modified	Weiser JD

Entities found in this pathway (9)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Hnrnpd	Q14103-3, Q14103-4	Hspa8	P11142	Psma2	P25787
Psma4	P25789	Psma6	P60900	Psmb10	P40306
Psmb3	P49720	Psmb4	P28070	Psmc3	P17980

16. Programmed Cell Death (R-HSA-5357801)



Cell death is a fundamental cellular response that has a crucial role in shaping our bodies during development and in regulating tissue homeostasis by eliminating unwanted cells. There are a number of different forms of cell death, each with a corresponding number of complex subprocesses. The first form of regulated or programmed cell death to be characterized was apoptosis. Evidence has emerged for a number of regulated non-apoptotic cell death pathways, including some with morphological features that were previously attributed to necrosis. More recently necrosis has been subdivided into parts including programmed necrotic cell death processes, such as RIP1-mediated regulated necrosis or pyroptosis.

Reactome currently represents programmed cell death using the model of extrinsic signalling that leads to a molecular decision point pivoting on caspase-8 activation or inhibition. Caspase-8 activation tilts the cell towards apoptosis, while caspase-8 inhibition tilts the cell towards Regulated Necrosis.

The terminology and molecular definitions of cell death-related events annotated here are consistent with the 2015 recommendations of the Nomenclature Committee on Cell Death (NCCD) (Galluzzi L et al. 2015).

References

Galluzzi L, Bravo-San Pedro JM, Vitale I, Aaronson SA, Abrams JM, Adam D, ... Kroemer G (2015). Essential versus accessory aspects of cell death: recommendations of the NCCD 2015. Cell Death Differ., 22, 58-73.

Edit history

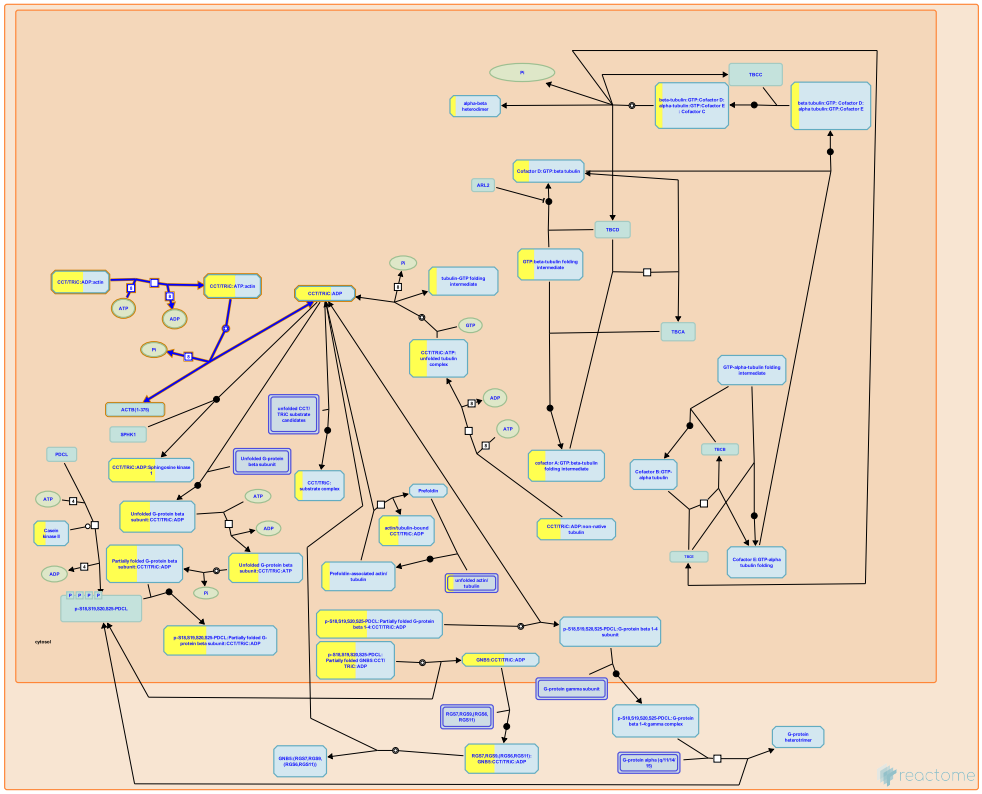
Date	Action	Author
2014-03-26	Created	Shamovsky V
2014-11-18	Edited	Shamovsky V
2014-11-18	Authored	Shamovsky V

Date	Action	Author
2021-09-10	Modified	Weiser JD

Entities found in this pathway (18)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
C1qbp	Q07021	Casp1	P29466, P51878	Cdc37	Q16543
Cdh1	P12830	Dbnl	Q9UJU6	Kpnb1	Q14974
Psma2	P25787	Psma4	P25789	Psma6	P60900
Psmb10	P40306	Psmb3	P49720	Psmb4	P28070
Psmc3	P17980	Ywhae	P62258	Ywhag	P61981
Ywhah	Q04917	Ywhaq	P27348	Ywhaz	P63104

17. Folding of actin by CCT/TriC (R-HSA-390450)



Cellular compartments: cytosol.

Nucleotide-independent transfer of beta-actin from prefoldin to CCT occurs when prefoldin binds to CCT (Vainberg et al., 1998). Following ATP- dependent folding within CCT (Gao et al., 1992), beta-actin is released as a soluble, monomeric protein.

References

Gao Y, Thomas JO, Chow RL, Lee GH & Cowan NJ (1992). A cytoplasmic chaperonin that catalyzes beta-actin folding. Cell, 69, 1043-50.

Melki R, Vainberg IE, Chow RL & Cowan NJ (1993). Chaperonin-mediated folding of vertebrate actin-related protein and gamma-tubulin. J Cell Biol, 122, 1301-10.

Vainberg IE, Lewis SA, Rommelaere H, Ampe C, Vandekerckhove J, Klein HL & Cowan NJ (1998). Prefoldin, a chaperone that delivers unfolded proteins to cytosolic chaperonin. Cell, 93, 863-73.

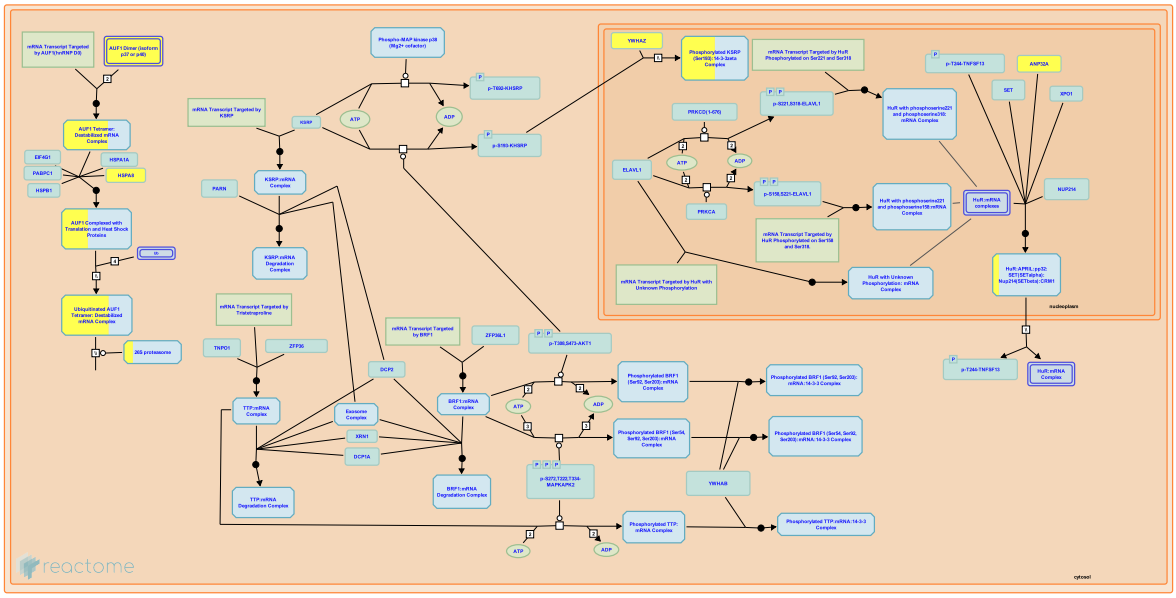
Edit history

Date	Action	Author
2008-12-01	Authored	Matthews L
2009-01-21	Reviewed	Cowan NJ
2009-02-09	Created	Matthews L
2009-02-21	Edited	Matthews L
2017-05-16	Modified	Matthews L

Entities found in this pathway (6)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Cct2	P78371	Cct3	P49368	Cct4	P50991
Cct7	Q99832	Cct8	P50990	Tcp1	P17987

18. Regulation of mRNA stability by proteins that bind AU-rich elements (R-HSA-450531)



Cellular compartments: cytosol, nucleoplasm.

RNA elements rich in adenine and uracil residues (AU-rich elements) bind specific proteins which either target the RNA for degradation or, more rarely, stabilize the RNA. The activity of the AU-element binding proteins is regulated, usually by phosphorylation but also by subcellular localization.

References

Barreau C, Paillard L & Osborne HB (2005). AU-rich elements and associated factors: are there unifying principles?. Nucleic Acids Res, 33, 7138-50.

Bevilacqua A, Ceriani MC, Capaccioli S & Nicolin A (2003). Post-transcriptional regulation of gene expression by degradation of messenger RNAs. J Cell Physiol, 195, 356-72.

Zhang T, Kruys V, Huez G & Gueydan C (2002). AU-rich element-mediated translational control: complexity and multiple activities of trans-activating factors. Biochem Soc Trans, 30, 952-8.

Gingerich TJ, Feige JJ & LaMarre J (2004). AU-rich elements and the control of gene expression through regulated mRNA stability. Anim Health Res Rev, 5, 49-63.

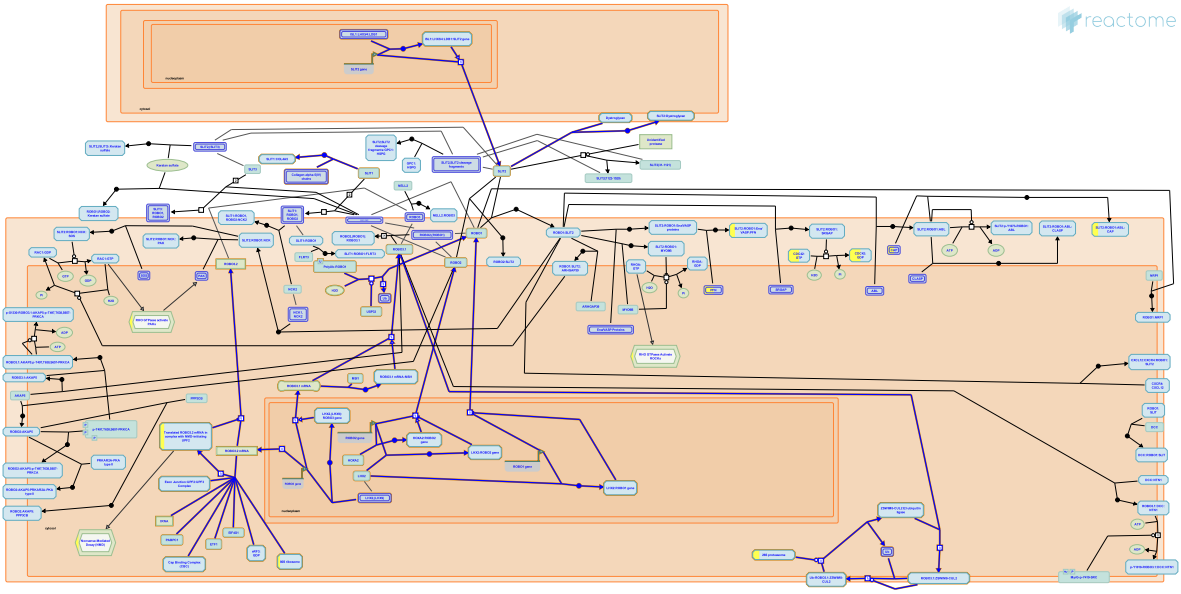
Edit history

Date	Action	Author
2009-12-17	Created	May B
2009-12-29	Edited	May B
2009-12-29	Authored	May B
2010-06-29	Reviewed	Wilusz J
2021-09-10	Modified	Weiser JD

Entities found in this pathway (11)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Anp32a	P39687	Hnrnpd	Q14103-3, Q14103-4	Hspa8	P11142
Psma2	P25787	Psma4	P25789	Psma6	P60900
Psmb10	P40306	Psmb3	P49720	Psmb4	P28070
Psmc3	P17980	Ywhaz	P63104		

19. Regulation of expression of SLITs and ROBOs (R-HSA-9010553)



Expression of SLIT and ROBO proteins is regulated at the level of transcription, translation and protein localization and stability. LIM-homeodomain transcription factors LHX2, LHX3, LHX4, LHX9 and ISL1 have so far been implicated in a cell type-dependent transcriptional regulation of ROBO1, ROBO2, ROBO3 and SLIT2 (Wilson et al. 2008, Marcos-Mondejar et al. 2012, Kim et al. 2016). Homeobox transcription factor HOXA2 is involved in transcriptional regulation of ROBO2 (Geisen et al. 2008). Transcription of SLIT1 during optic tract development in Xenopus is stimulated by FGF signaling and may also involve the transcription factor HOXA2, but the mechanism has not been established (Atkinson-Leadbeater et al. 2010). PAX6 and the homeodomain transcription factor NKX2.2 are also implicated in regulation of SLIT1 transcription (Genethliou et al. 2009). An RNA binding protein, MSI1, binds ROBO3 mRNA and promotes its translation, thus increasing ROBO3 protein levels (Kuwako et al. 2010). A poorly studied E3 ubiquitin ligase ZSWIM8 promotes degradation of ROBO3 (Wang et al. 2013). ROBO1 is protein half-life is increased via deubiquitination of ROBO1 by a ubiquitin protease USP33 (Yuasa-Kawada et al. 2009, Huang et al. 2015). Interaction of SLIT2 with DAG1 (dystroglycan) is important for proper localization of SLIT2 at the floor plate (Wright et al. 2012). Interaction of SLIT1 with a type IV collagen COL4A5 is important for localization of SLIT1 to the basement membrane of the optical tectum (Xiao et al. 2011).

References

Wilson SI, Shafer B, Lee KJ & Dodd J (2008). A molecular program for contralateral trajectory: Rig-1 control by LIM homeodomain transcription factors. Neuron, 59, 413-24.

Marcos-Mondéjar P, Peregrín S, Li JY, Carlsson L, Tole S & López-Bendito G (2012). The lhx2 transcription factor controls thalamocortical axonal guidance by specific regulation of robo1 and robo2 receptors. J. Neurosci., 32, 4372-85.

Kim KT, Kim N, Kim HK, Lee H, Gruner HN, Gergics P, ... Song MR (2016). ISL1-based LIM complexes control Slit2 transcription in developing cranial motor neurons. Sci Rep, 6, 36491.

Geisen MJ, Di Meglio T, Pasqualetti M, Ducret S, Brunet JF, Chédotal A & Rijli FM (2008). Hox paralog group 2 genes control the migration of mouse pontine neurons through slit-robo signaling. PLoS Biol., 6, e142.

Kuwako K, Kakumoto K, Imai T, Igarashi M, Hamakubo T, Sakakibara S, ... Okano H (2010). Neural RNA-binding protein Musashi1 controls midline crossing of precerebellar neurons through posttranscriptional regulation of Robo3/Rig-1 expression. Neuron, 67, 407-21.

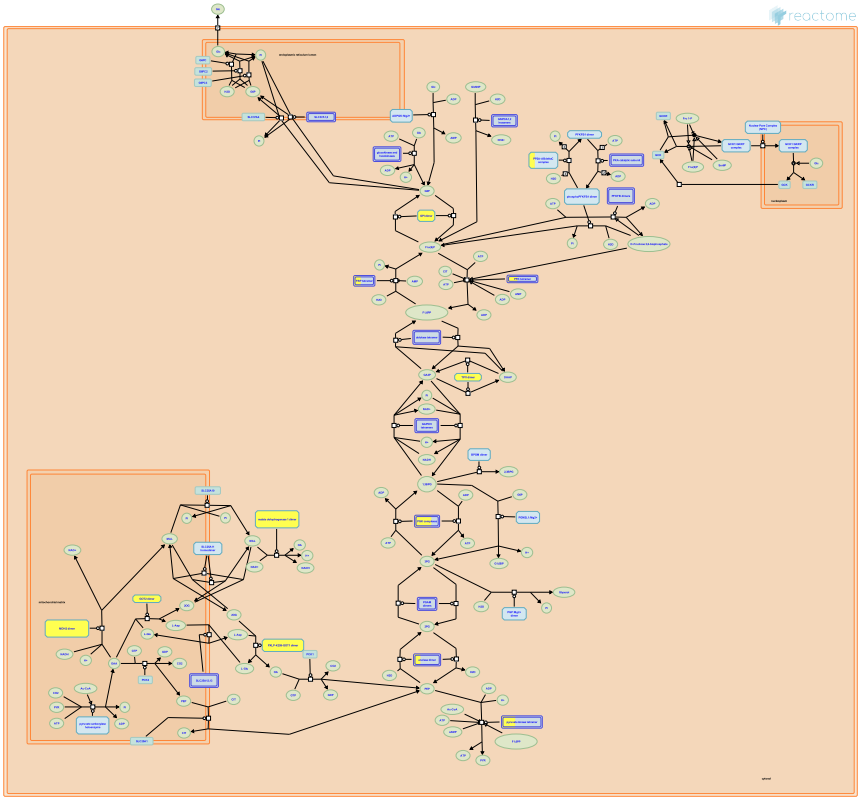
Edit history

Date	Action	Author
2017-06-27	Authored	Orlic-Milacic M
2017-06-27	Created	Orlic-Milacic M
2017-07-31	Reviewed	Jaworski A
2017-08-04	Edited	Orlic-Milacic M
2021-09-10	Modified	Weiser JD

Entities found in this pathway (16)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Psma2	P25787	Psma4	P25789	Psma6	P60900
Psmb10	P40306	Psmb3	P49720	Psmb4	P28070
Psmc3	P17980	RPS13	P62277	RPS3A	P61247
Rpl18	Q07020	Rpl30	P62888	Rpl4	P36578
Rplp1	P05386	Rps5	P46782	Rps7	P62081
Rps9	P46781				

20. Glucose metabolism (R-HSA-70326)



Glucose is the major form in which dietary sugars are made available to cells of the human body. Its breakdown is a major source of energy for all cells, and is essential for the brain and red blood cells. Glucose utilization begins with its uptake by cells and conversion to glucose 6-phosphate, which cannot traverse the cell membrane. Fates open to cytosolic glucose 6-phosphate include glycolysis to yield pyruvate, glycogen synthesis, and the pentose phosphate pathway. In some tissues, notably the liver and kidney, glucose 6-phosphate can be synthesized from pyruvate by the pathway of gluconeogenesis.

References

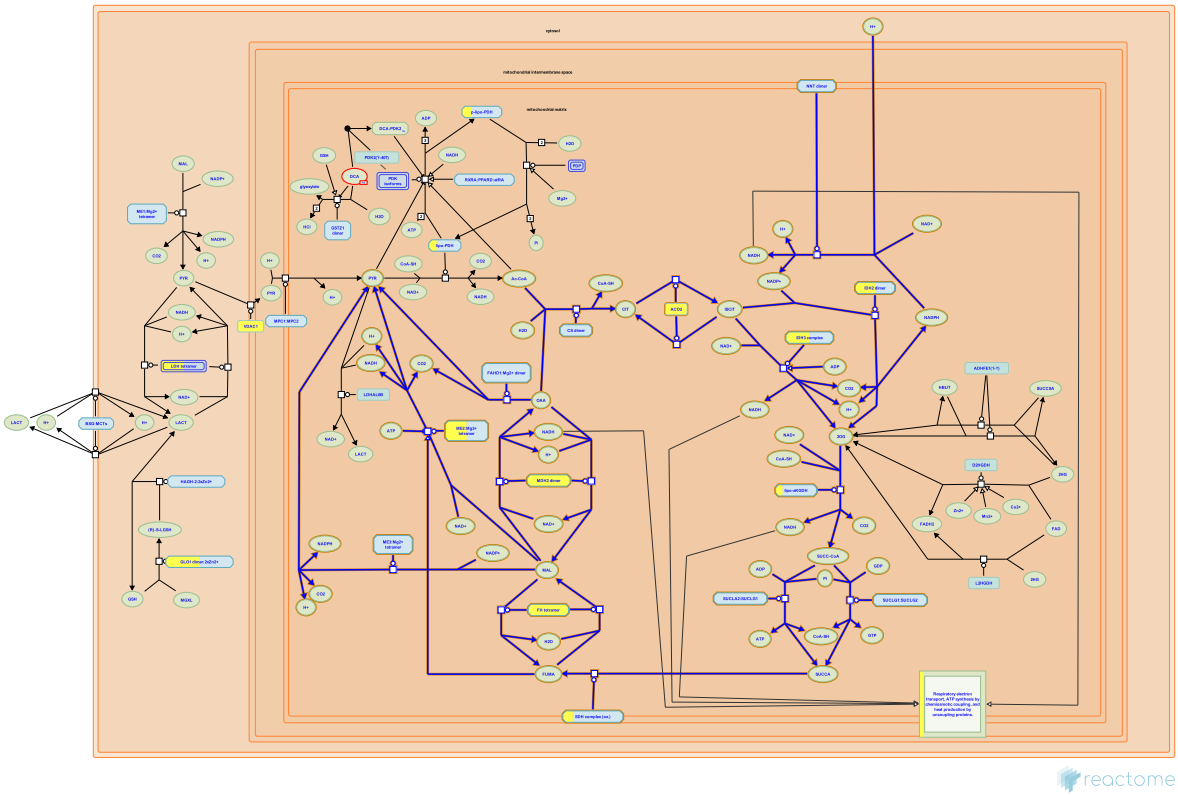
Edit history

Date	Action	Author
2003-02-05	Authored	Schmidt EE
2009-12-12	Revised	D'Eustachio P
2021-08-26	Edited	D'Eustachio P
2021-09-10	Modified	Weiser JD

Entities found in this pathway (11)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Eno1	P06733	Fbp2	O00757	Got1	P17174
Got2	P00505	Gpi	P06744	Mdh1	P40925, P40926
Pfkp	Q01813	Pgk1	P00558, P07205	Pkm	P14618-1, P14618-2
Ppp2r1a	P30153	Tpi1	P60174		

21. Citric acid cycle (TCA cycle) (R-HSA-71403)



Cellular compartments: mitochondrion.

In the citric acid or tricarboxylic acid (TCA) cycle, the acetyl group of acetyl CoA (derived primarily from oxidative decarboxylation of pyruvate, beta-oxidation of long-chain fatty acids, and catabolism of ketone bodies and several amino acids) can be completely oxidized to CO2 in reactions that also yield one high-energy phosphate bond (as GTP or ATP) and four reducing equivalents (three NADH + H+, and one FADH2). The NADH and FADH2 are then oxidized by the electron transport chain to yield nine more high-energy phosphate bonds (as ATP). All reactions of the citric acid cycle take place in the mitochondrion.

Eight canonical reactions mediate the synthesis of citrate from acetyl-CoA and oxaloacetate and the metabolism of citrate to re-form oxaloacetate. Six additional reactions are included here. Three reversible reactions, the interconversions of citrate and isocitrate, of fumarate and malate, and of malate and oxaloacetate are annotated in both their canonical (forward) and reverse directions. The synthesis of succinate from succinyl-CoA can be coupled to the phosphorylation of either GDP (the canonical reaction) or ADP; both reactions are annotated. Two mitochondrial isocitrate dehydrogenase isozymes catalyze the oxidative decarboxylation of isocitrate to form alpha-ketoglutarate (2-oxoglutarate): IDH3 catalyzes the canonical reaction coupled to the reduction of NAD+, while IDH2 catalyzes the same reaction coupled to reduction of NADP+, a reaction whose normal physiological function is unclear. Both reactions are annotated. Finally, a reaction is annotated in which reducing equivalents are transferred from NADPH to NAD+ coupled to proton import across the inner mitochondrial membrane.

The cyclical nature of the reactions responsible for the oxidation of acetate was first suggested by Hans Krebs, from biochemical studies of pigeon breast muscle (Krebs et al. 1938; Krebs and Eggleston 1940). Many of the molecular details of individual reactions were worked out by Ochoa and colleagues, largely through studies of enzymes purified from pig heart (Ochoa 1980). While the human homologues of these enzymes have all been identified, their biochemical characterization has in general been limited and many molecular details of the human reactions are inferred from those worked out in studies of the model systems.

References

Krebs HA & Eggleston LV (1940). The oxidation of pyruvate in pigeon breast muscle. Biochem J, 34, 442-459.

Krebs HA, Salvin E & Johnson WA (1938). The formation of citric and alpha-ketoglutaric acids in the mammalian body. Biochem J, 32, 113-117.

Ochoa S (1980). The pursuit of a hobby. Annu Rev Biochem, 49, 1-30.

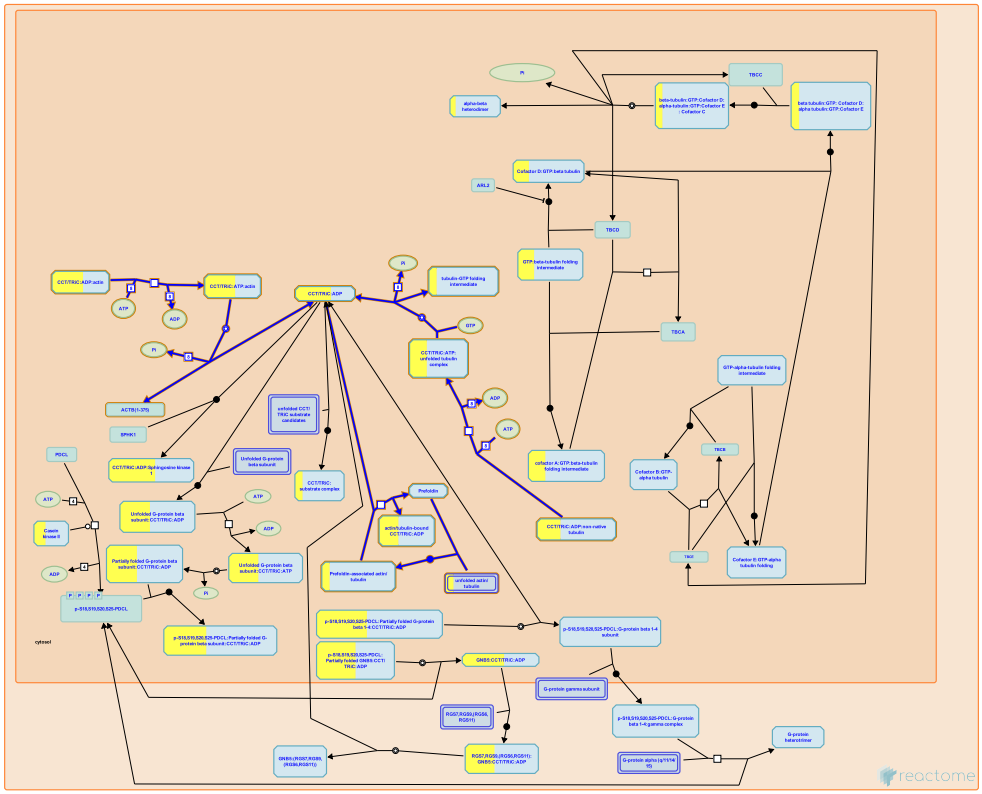
Edit history

Date	Action	Author
2003-01-28	Authored	Birney E
2009-12-26	Revised	D'Eustachio P
2021-08-26	Edited	D'Eustachio P
2021-09-20	Modified	Weiser JD

Entities found in this pathway (9)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Aco1	Q99798	Dld	P09622	Fh	P07954
Idh1	P51553	Idh2	P48735, P50213	Idh3g	P51553
Mdh1	P40926	Me2	P23368	Sdhb	P21912

22. Cooperation of Prefoldin and TriC/CCT in actin and tubulin folding (R-HSA-389958)



Cellular compartments: cytosol.

In the case of actin and tubulin folding, and perhaps other substrates, the emerging polypeptide chain is transferred from the ribosome to TRiC via Prefoldin (Vainberg et al., 1998).

References

Vainberg IE, Lewis SA, Rommelaere H, Ampe C, Vandekerckhove J, Klein HL & Cowan NJ (1998). Prefoldin, a chaperone that delivers unfolded proteins to cytosolic chaperonin. Cell, 93, 863-73.

Edit history

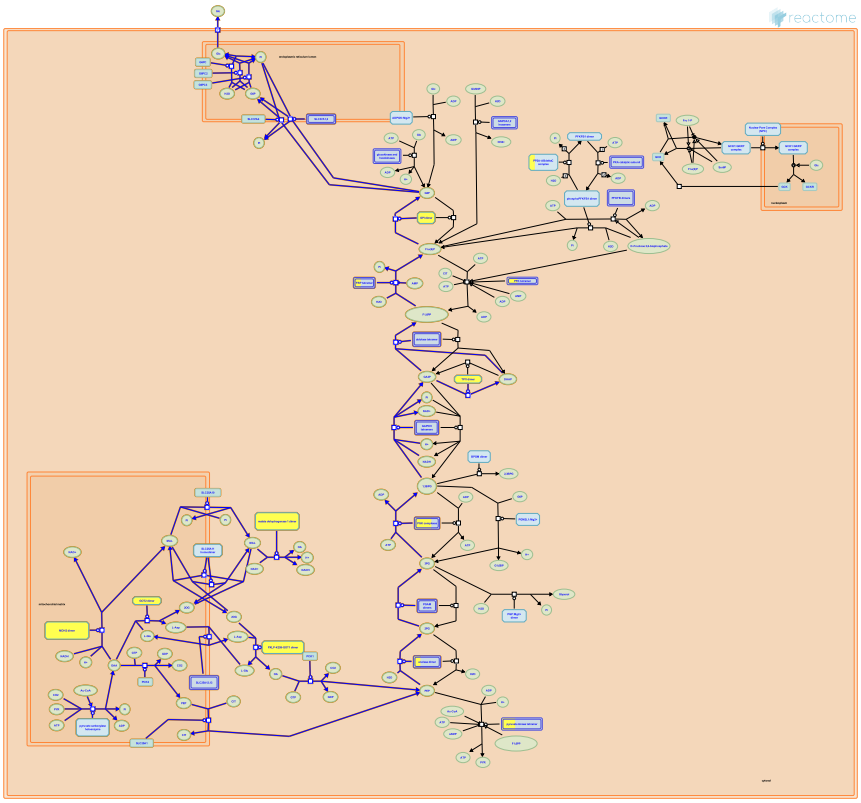
Date	Action	Author
2008-12-01	Authored	Matthews L
2009-01-21	Reviewed	Cowan NJ
2009-01-22	Created	Matthews L
2009-02-21	Edited	Matthews L
2017-03-03	Modified	Matthews L

Entities found in this pathway (7)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Cct2	P78371	Cct3	P49368	Cct4	P50991
Cct7	Q99832	Cct8	P50990	Tcp1	P17987

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Tubb4b	P04350, P68371				

23. Gluconeogenesis (R-HSA-70263)



The reactions of gluconeogenesis convert mitochondrial pyruvate to cytosolic glucose 6-phosphate which in turn can be hydrolyzed to glucose and exported from the cell. Gluconeogenesis is confined to cells of the liver and kidney and enables glucose synthesis from molecules such as lactate and alanine and other amino acids when exogenous glucose is not available (reviewed, e.g., by Gerich 1993). The process of gluconeogenesis as diagrammed below occurs in two parts: a network of reactions converts mitochondrial pyruvate to cytosolic phosphoenolpyruvate; then phosphoenolpyruvate is converted to glucose 6-phosphate in a single sequence of cytosolic reactions.

Three variants of the first part of the process are physiologically important. 1) A series of transport and transamination reactions convert mitochondrial oxaloacetate to cytosolic oxaloacetate which is converted to phosphoenolpyruvate by a hormonally regulated, cytosolic isoform of phosphoenolpyruvate carboxykinase. This variant allows regulated glucose synthesis from lactate. 2) Mitochondrial oxaloacetate is reduced to malate, which is exported to the cytosol and re-oxidized to oxaloacetate. This variant provides reducing equivalents to the cytosol, needed for glucose synthesis from amino acids such as alanine and glutamine. 3) Constitutively expressed mitochondrial phosphoenolpyruvate carboxykinase catalyzes the conversion of mitochondrial oxaloacetate to phosphoenolpyruvate which is then transported to the cytosol. The exact path followed by any one molecule of pyruvate through this reaction network is determined by the tissue in which the reactions are occurring, the source of the pyruvate, and the physiological stress that triggered gluconeogenesis.

In all cases, the synthesis of glucose from two molecules of pyruvate requires the generation and consumption of two reducing equivalents as cytosolic NADH + H+. For pyruvate derived from lactate (variants 1 and 3), NADH + H+ is generated with the oxidation of lactate to pyruvate in the cytosol (a reaction of pyruvate metabolism not shown in the diagram). For pyruvate derived from amino acids (variant 2), mitochondrial NADH + H+ generated by glutamate dehydrogenase (a reaction of amino acid metabolism, not shown) is used to reduce oxaloacetate to malate, which is transported to the cytosol and re-oxidized, generating cytosolic NADH + H+. The synthesis of glucose from pyruvate also requires the consumption of six high-energy phosphates, four from ATP and two from GTP.

In the second part of gluconeogenesis, cytosolic phosphoenolpyruvate, however derived, is converted to fructose 1,6-bisphosphate by reactions that are the reverse of steps of glycolysis. Hydrolysis of fructose 1,6-bisphosphate to fructose 6-phosphate is catalyzed by fructose 1,6-bisphosphatase, and fructose 6-phosphate is reversibly isomerized to glucose 6-phosphate.

References

Gerich JE (1993). Control of glycaemia. Baillieres Clin Endocrinol Metab, 7, 551-86.

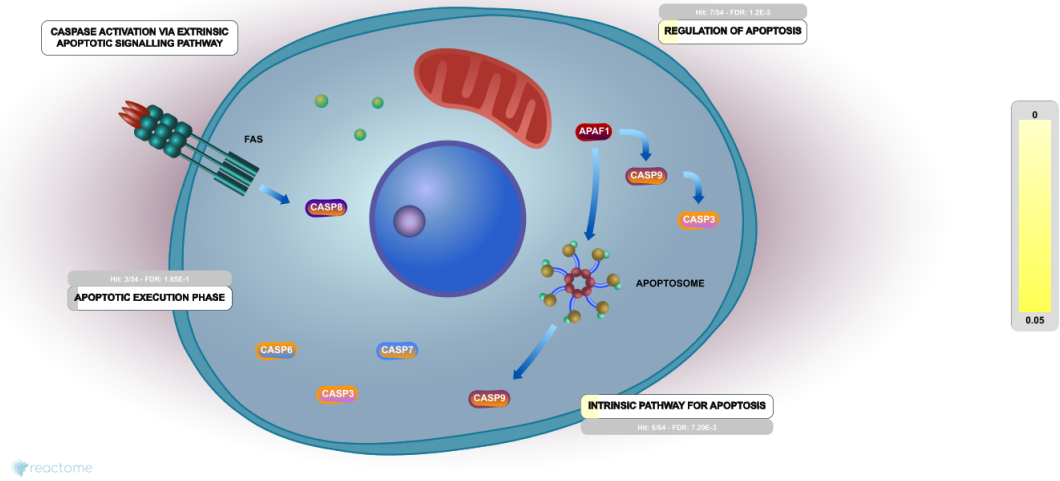
Edit history

Date	Action	Author
2008-09-10	Reviewed	Harris RA
2008-09-13	Revised	D'Eustachio P
2021-08-26	Edited	D'Eustachio P
2021-09-20	Modified	Weiser JD

Entities found in this pathway (8)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Eno1	P06733	Fbp2	O00757	Got1	P17174
Got2	P00505	Gpi	P06744	Mdh1	P40925, P40926
Pgk1	P00558, P07205	Tpi1	P60174		

24. Apoptosis (R-HSA-109581)



Apoptosis is a distinct form of cell death that is functionally and morphologically different from necrosis. Nuclear chromatin condensation, cytoplasmic shrinking, dilated endoplasmic reticulum, and membrane blebbing characterize apoptosis in general. Mitochondria remain morphologically unchanged. In 1972 Kerr et al introduced the concept of apoptosis as a distinct form of "cell-death", and the mechanisms of various apoptotic pathways are still being revealed today.

The two principal pathways of apoptosis are (1) the Bcl-2 inhibitable or intrinsic pathway induced by various forms of stress like intracellular damage, developmental cues, and external stimuli and (2) the caspase 8/10 dependent or extrinsic pathway initiated by the engagement of death receptors

The caspase 8/10 dependent or extrinsic pathway is a death receptor mediated mechanism that results in the activation of caspase-8 and caspase-10. Activation of death receptors like Fas/CD95, TNFR1, and the TRAIL receptor is promoted by the TNF family of ligands including FASL (APO1L OR CD95L), TNF, LT-alpha, LT-beta, CD40L, LIGHT, RANKL, BLYS/BAFF, and APO2L/TRAIL. These ligands are released in response to microbial infection, or as part of the cellular, humoral immunity responses during the formation of lymphoid organs, activation of dendritic cells, stimulation or survival of T, B, and natural killer (NK) cells, cytotoxic response to viral infection or oncogenic transformation.

The Bcl-2 inhibitable or intrinsic pathway of apoptosis is a stress-inducible process, and acts through the activation of caspase-9 via Apaf-1 and cytochrome c. The rupture of the mitochondrial membrane, a rapid process involving some of the Bcl-2 family proteins, releases these molecules into the cytoplasm. Examples of cellular processes that may induce the intrinsic pathway in response to various damage signals include: auto reactivity in lymphocytes, cytokine deprivation, calcium flux or cellular damage by cytotoxic drugs like taxol, deprivation of nutrients like glucose and growth factors like EGF, anoikis, transactivation of target genes by tumor suppressors including p53.

In many non-immune cells, death signals initiated by the extrinsic pathway are amplified by connections to the intrinsic pathway. The connecting link appears to be the truncated BID (tBID) protein a proteolytic cleavage product mediated by caspase-8 or other enzymes.

References

MacFarlane M & Williams AC (2004). Apoptosis and disease: a life or death decision. EMBO Rep, 5, 674-8.

Kerr JF, Wyllie AH & Currie AR (1972). Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer, 26, 239-57.

Kerr JF (2002). History of the events leading to the formulation of the apoptosis concept. Toxicology , 181, 471-4.

Adams JM (2003). Ways of dying: multiple pathways to apoptosis. Genes Dev, 17, 2481-95.

Cory S, Huang DC & Adams JM (2003). The Bcl-2 family: roles in cell survival and oncogenesis. Oncogene, 22, 8590-607.

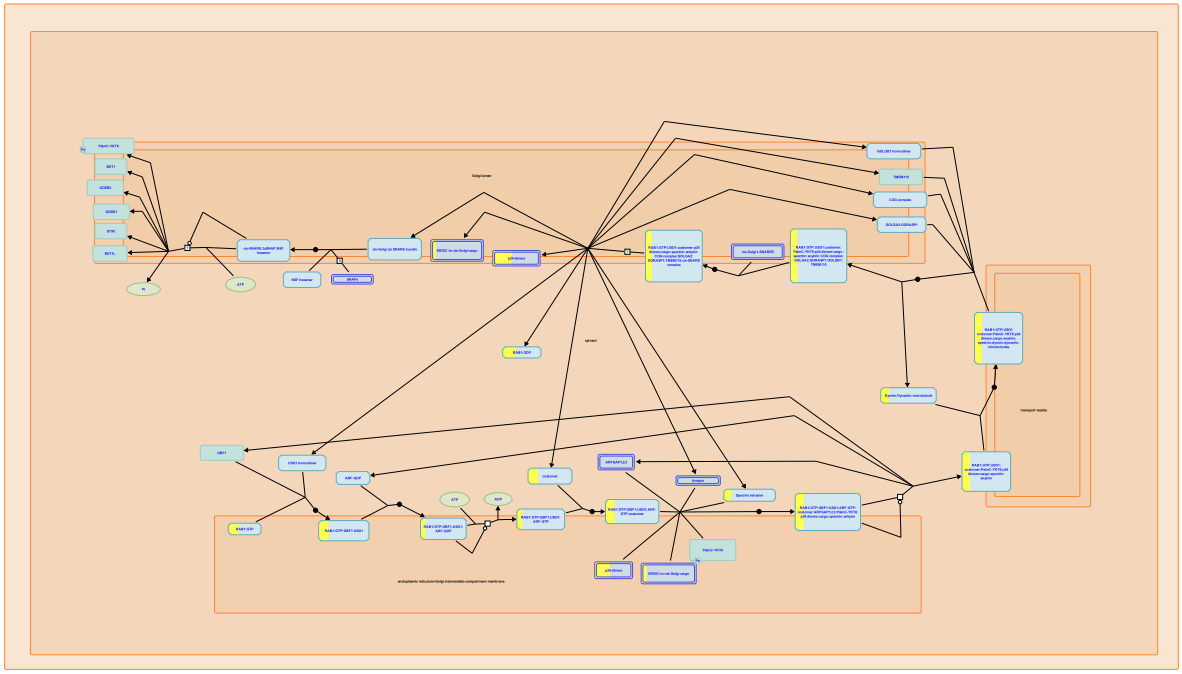
Edit history

Date	Action	Author
2004-01-16	Authored	Tsujimoto Y, Hengartner M, Hardwick JM, Tschopp J, Alnemri E
2004-01-16	Created	Tsujimoto Y, Hengartner M, Hardwick JM, Tschopp J, Alnemri E
2013-11-25	Edited	Joshi-Tope G, Matthews L, Gopinathrao G, Gillespie ME
2021-08-26	Reviewed	Ranganathan S, Hengartner M, Vaux DL
2021-09-10	Modified	Weiser JD

Entities found in this pathway (16)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
C1qbp	Q07021	Cdh1	P12830	Dbnl	Q9UJU6
Kpnb1	Q14974	Psma2	P25787	Psma4	P25789
Psma6	P60900	Psmb10	P40306	Psmb3	P49720
Psmb4	P28070	Psmc3	P17980	Ywhae	P62258
Ywhag	P61981	Ywhah	Q04917	Ywhaq	P27348
Ywhaz	P63104				

25. COPI-mediated anterograde transport (R-HSA-6807878)



The ERGIC (ER-to-Golgi intermediate compartment, also known as vesicular-tubular clusters, VTCs) is a stable, biochemically distinct compartment located adjacent to ER exit sites (Ben-Tekaya et al, 2005; reviewed in Szul and Sztul, 2011). The ERGIC concentrates COPII-derived cargo from the ER for further anterograde transport to the cis-Golgi and also recycles resident ER proteins back to the ER through retrograde traffic. Both of these pathways appear to make use of microtubule-directed COPI-coated vesicles (Pepperkok et al, 1993; Presley et al, 1997; Scales et al, 1997; Stephens and Pepperkok, 2002; Stephens et al, 2000; reviewed in Lord et al, 2001; Spang et al, 2013).

References

Ben-Tekaya H, Miura K, Pepperkok R & Hauri HP (2005). Live imaging of bidirectional traffic from the ERGIC. J. Cell. Sci., 118, 357-67.

Szul T & Sztul E (2011). COPII and COPI traffic at the ER-Golgi interface. Physiology (Bethesda), 26, 348-64.

Pepperkok R, Scheel J, Horstmann H, Hauri HP, Griffiths G & Kreis TE (1993). Beta-COP is essential for biosynthetic membrane transport from the endoplasmic reticulum to the Golgi complex in vivo. Cell, 74, 71-82.

Presley JF, Cole NB, Schroer TA, Hirschberg K, Zaal KJ & Lippincott-Schwartz J (1997). ER-to-Golgi transport visualized in living cells. Nature, 389, 81-5.

Scales SJ, Pepperkok R & Kreis TE (1997). Visualization of ER-to-Golgi transport in living cells reveals a sequential mode of action for COPII and COPI. Cell, 90, 1137-48.

Edit history

Date	Action	Author
2015-09-01	Edited	Rothfels K
2015-09-01	Authored	Rothfels K

Date	Action	Author
2015-09-02	Reviewed	Gillespie ME
2015-11-03	Created	Rothfels K
2021-09-10	Modified	Weiser JD

Entities found in this pathway (11)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Cap1	P47755	Capza1	P52907	Capza2	P47755
Copb1	P53618	Copg1	Q9Y678	Dync1h1	Q14204
Rab1A	P62820	Sptbn1	Q01082	Tmed10	P49755
Tmed9	Q9BVK6	Tubb4b	P04350, P68371, Q3ZCM7		

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.

Entities (194)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Acaa2	P42765	Acadvl	P49748	Acly	P53396
Aco1	Q99798	Actg2	P63267	Actr3	P61158
Ahsg	P02765	Akr7a3	O43488, O95154	Aldh2	P05091
Aldh3a2	P51648-1, P51648-2	Anp32a	P39687	Anxa2	P07355
Ap1b1	Q10567	Ap2b1	P63010	Aprt	P07741
Asah1	Q13510	B2m	P61769	Banf1	O75531
C1qbp	Q07021	Cand1	Q86VP6	Cap1	Q01518
Capg	Q9BPX3	Capn1	P07384	Capza1	P52907
Capza2	P47755	Casp1	P29466, P51878	Cav1	Q03135
Cct2	P78371	Cct3	P49368	Cct4	P50991
Cct7	Q99832	Cct8	P50990	Cdc37	Q16543
Cdc42	P60953	Cdh1	Q9UM11	Ckb	P12277
Col6a5	A8TX70	Copb1	P53618	Copg1	Q9Y678
Cpne3	O75131	Cryl1	Q9Y2S2	Csnk2b	P67870
Ctnnd1	O60716	Ctsa	P10619	Ctsc	P53634
Cyb5b	O43169, P00167	Dbnl	Q9UJU6	Ddx17	Q92841
Ddx39b	Q13838	Dhx15	O43143	Dhx9	Q08211
Dlat	P10515	Dld	P09622	Dync1h1	Q14204
Eef1a1	P68104	Efhd2	Q96C19	Ehd2	Q9NZN3, Q9NZN4
Eno1	P06733	Epb41l2	O43491	Epb41l3	Q9Y2J2
Epcam	P16422	Eprs	P07814	Etfa	P13804
Fbp2	O00757	Fh	P07954	Fis1	Q9Y3D6
Flnb	O75369	Fth1	P02794	G6pdx	P11413
Gdi1	P50395	Gdi2	P50395	Glo1	Q04760
Got1	P17174	Got2	P00505	Gpi	P06744
Gpx3	O75715, P22352	Gsr	P00390-1, P00390-2	Gstm2	P09488, P28161
Hadh	P40939, Q16836	Hadha	P40939	Hdlbp	Q00341
Hnrnpa2b1	P22626	Hnrnpc	P07910	Hnrnpd	Q14103, Q14103-3, Q14103-4
Hnrnpf	P52597	Hnrnph2	P55795	Hsd17b10	Q99714
Hspa2	P54652	Hspa4	P34932	Hspa8	P11142
Hspa9	P38646	Idh1	O75874	Idh2	P48735, P50213
Idh3g	P51553	Ighm	P01871	Iqgap1	P46940
Kpnb1	Q14974	Lamb1	P07942	Lap3	Q13867
Ldha	P00338	Ldhb	P07195	Lypla2	O95372
Manf	P55145	Mdh1	P40926	Me2	P23368
Mfap4	P55083	Mogs	Q13724	Mpst	P25325
Mtco2	P00403	Mttp	P55157	Myl12b	O14950
Nans	Q9NR45	Ncl	P19338	Ndrg1	Q92597
Ndufab1	O14561	Ndufs2	O75306	Ndufv2	P19404
Nedd4	P46934	Nme2	P22392	Npm1	P06748
Pdia6	Q15084	Pdlim5	Q96HC4	Pdxk	O00764

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
Pfkp	Q01813	Pfn1	P07737	Pgd	P52209
Pgk1	P00558, P07205	Pgls	O95336	Pgm1	P36871
Picalm	Q13492	Pitpna	Q00169	Pkm	P14618
Pla2g4c	Q9UP65	Plcb3	Q01970	Ppp2r1a	P30153
Prdx2	P32119	Prdx5	P30044-1, P30044-2	Psma2	P25787
Psma4	P25789	Psma6	P60900	Psmb10	P40306
Psmb3	P49720	Psmb4	P28070	Psmc3	P17980
Ptbp1	P26599	Ptgr1	Q14914	Ptgs1	P23219
Pycard	Q9ULZ3	RPS13	P62277	RPS3A	P61247
Rab1A	P62820	Rars1	P54136	Rlc-a	P19105
Rpl18	Q07020	Rpl30	P62888	Rpl4	P36578
Rplp1	P05386	Rps5	P46782	Rps7	P62081
Rps9	P46781	Rtcb	Q9Y3I0	S100a11	P31949
SNRPE	P62304	Sdhb	P21912	Sec23a	Q15436
Sept7	Q16181	Serpinb1a	P30740	Sfpq	P23246
Shmt1	P34896	Snd1	Q7KZF4	Snrpd2	P62316
Snrpd3	P62318	Sptbn1	Q01082	St13	P50502
Tagln2	P37802	Tapbp	O15533	Tcp1	P17987
Tgfbi	Q15582	Tln1	Q9Y490	Tmed10	P49755
Tmed9	Q9BVK6	Tpi1	P60174	Tsta3	Q13630
Tubb4b	P68371	Txndc5	Q8NBS9	Uqcr10	Q9UDW1
Uqcrh	P07919	Vdac1	P21796	Vps35	Q96QK1
Ywhae	P62258	Ywhag	P61981	Ywhah	Q04917
Ywhaq	P27348	Ywhaz	P63104		

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
Acadvl	ENSG00000072778	Acly	ENSG00000131473	Anxa2	ENSG00000182718
B2m	ENSG00000166710	Capza1	ENSG00000116489	Casp1	ENSG00000137752
Cav1	ENSG00000105974	Cdc42	ENSG00000070831	Fth1	ENST00000273550
Hnrnpa2b1	ENSG00000122566	Hnrnpf	ENSG00000169813	Hspa8	ENSG00000109971
Hspa9	ENSG00000113013	Ndrg1	ENSG00000104419	Pdia6	ENSG00000143870
Pitpna	ENSG00000174238	Tcp1	ENSG00000120438	Tln1	ENSG00000137076

7. Identifiers not found

These 29 identifiers were not found neither mapped to any entity in Reactome.

Ahsa1	Akr1c9	Anp32e	Anxa11	Calb2	Clic1	Ddx3y	Hnrnpul2
LOC100359503	LOC100362339	LOC100362366	LOC100362453	LOC100909441	LOC298795	Lpp	Lrrc59
Nap1l1	Ndufa13	Nutf2	Postn	Rbm39	Rnh1	Rps10l1	Scpep1
Serpinb5	Sh3bgrl	Sorbs2	Tppp3	Tpt1			