



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 83 on 10/03/2023. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMzAzMTAxMzI4NTZfNDI2NTc%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:

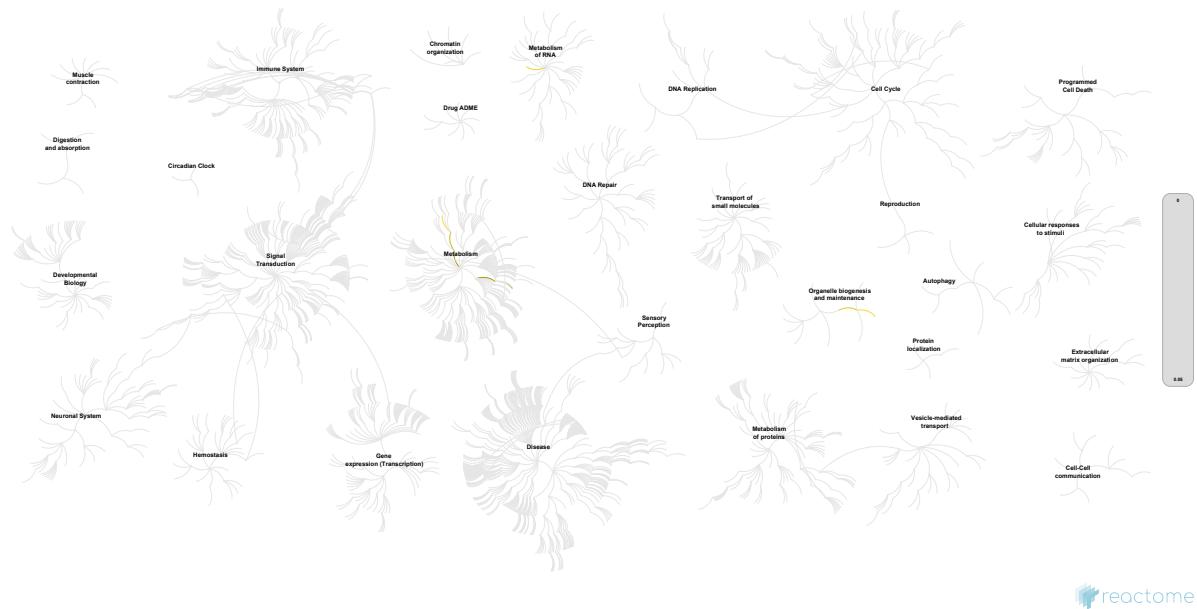
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 5 out of 20 identifiers in the sample were found in Reactome, where 29 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 'UniProt'.
- The unique ID for this analysis (token) is MjAyMzAzMTAxMzI4NTZfNDI2NTc%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
Formation of ATP by chemiosmotic coupling	2 / 18	0.002	4.90e-04	0.014	3 / 3	2.12e-04
Cristae formation	2 / 31	0.003	0.001	0.02	1 / 2	1.41e-04
Insulin-like Growth Factor-2 mRNA Binding Proteins (IGF2BPs/IMPs/VICKZs) bind RNA	1 / 3	2.57e-04	0.005	0.048	1 / 3	2.12e-04
Mitochondrial biogenesis	2 / 96	0.008	0.013	0.09	1 / 36	0.003
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins.	2 / 127	0.011	0.022	0.108	3 / 31	0.002
Lewis blood group biosynthesis	1 / 18	0.002	0.032	0.121	1 / 13	9.19e-04
Blood group systems biosynthesis	1 / 22	0.002	0.039	0.121	1 / 22	0.002
The citric acid (TCA) cycle and respiratory electron transport	2 / 178	0.015	0.04	0.121	3 / 67	0.005
Synthesis of active ubiquitin: roles of E1 and E2 enzymes	1 / 30	0.003	0.053	0.158	1 / 16	0.001
Organelle biogenesis and maintenance	2 / 298	0.026	0.1	0.199	1 / 86	0.006
Mitochondrial protein import	1 / 65	0.006	0.111	0.221	5 / 14	9.89e-04
Protein ubiquitination	1 / 80	0.007	0.135	0.26	1 / 32	0.002
MAPK6/MAPK4 signaling	1 / 89	0.008	0.149	0.26	2 / 40	0.003
HATs acetylate histones	1 / 108	0.009	0.177	0.26	1 / 15	0.001
Protein localization	1 / 166	0.014	0.26	0.26	5 / 53	0.004
Chromatin organization	1 / 240	0.021	0.354	0.354	1 / 85	0.006
Chromatin modifying enzymes	1 / 240	0.021	0.354	0.354	1 / 85	0.006
Metabolism of carbohydrates	1 / 300	0.026	0.421	0.421	1 / 241	0.017
Asparagine N-linked glycosylation	1 / 305	0.026	0.427	0.427	1 / 144	0.01
Antigen processing: Ubiquitination & Proteasome degradation	1 / 309	0.026	0.431	0.431	4 / 9	6.36e-04
MAPK family signaling cascades	1 / 338	0.029	0.461	0.461	2 / 122	0.009
Class I MHC mediated antigen processing & presentation	1 / 453	0.039	0.565	0.565	4 / 48	0.003
Metabolism of RNA	1 / 719	0.062	0.737	0.737	1 / 189	0.013
Post-translational protein modification	2 / 1,430	0.123	0.748	0.748	2 / 538	0.038

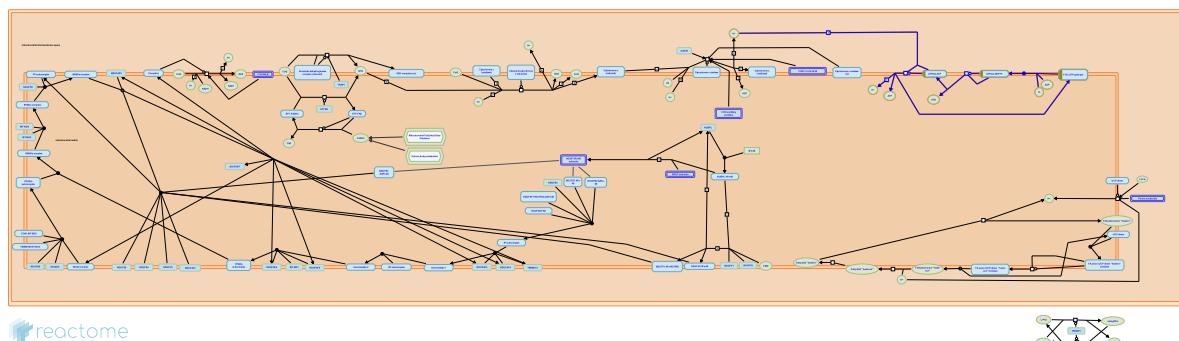
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Metabolism	3 / 2,143	0.184	0.769	0.769	4 / 2,268	0.16

* False Discovery Rate

5. Pathways details

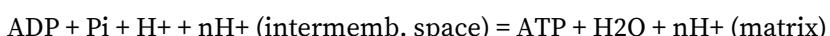
For every pathway of the most significant pathways, we present its diagram, as well as a short summary, its bibliography and the list of inputs found in it.

1. Formation of ATP by chemiosmotic coupling (R-HSA-163210)



The re-entry of protons into the mitochondrial matrix through Complex V causes conformational changes which result in ATP synthesis. Complex V (ATP synthase) is composed of 3 parts; an F1 catalytic core (approx 5 subunits), an F0 membrane proton channel (approx 9 subunits) and two stalks linking F1 to F0. F1 contains three alpha subunits, three beta subunits, and one each of gamma, delta, and epsilon subunits. Each beta subunit contains an active site for ATP synthesis. F0 has at least 9 subunits (a-g, A6L and F6), with one copy each of subunits b, d and F6.

The mechanism of ATP synthesis by Complex V was predicted by Boyer et al in 1973: ADP and Pi bind to the enzyme resulting in a conformational change. ATP is then synthesized, still bound to the enzyme. Another change in the active site results in the release of free ATP into the matrix. The overall reaction is:



References

Boyer PD, Momsen W & Cross RL (1973). A new concept for energy coupling in oxidative phosphorylation based on a. Proc Natl Acad Sci U S A, 70, 2837-9. [View](#)

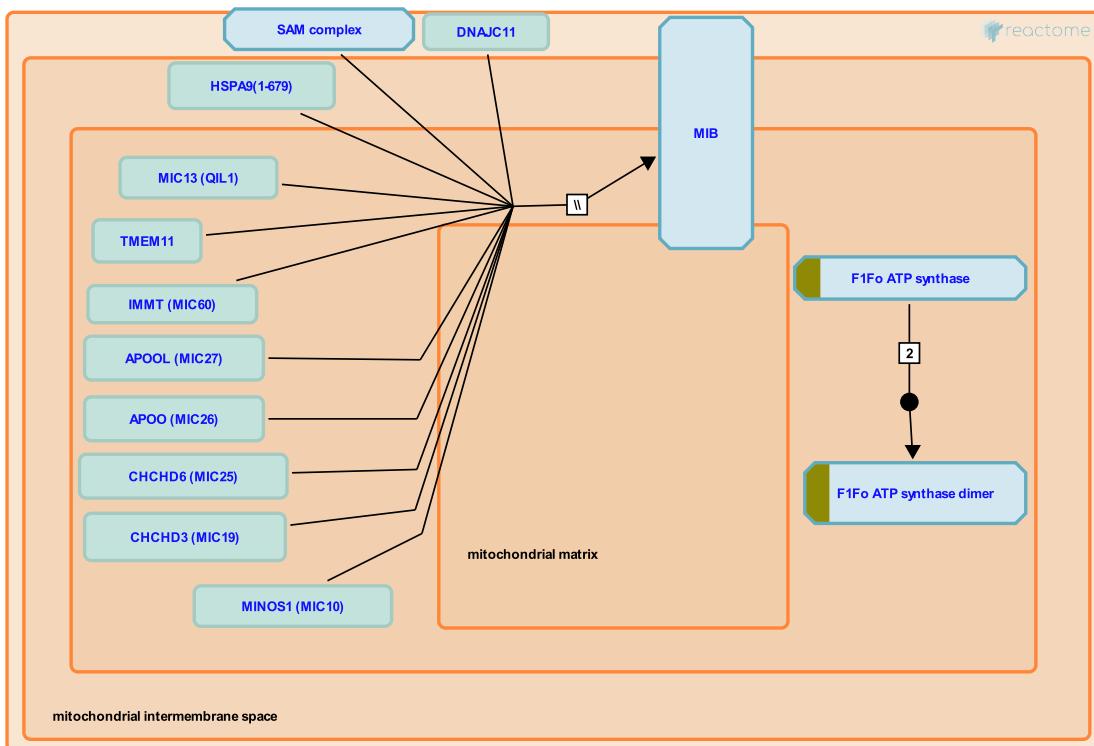
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Date	Action	Author
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2005-06-29	Authored	Jassal B
2022-11-19	Modified	Wright A

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

Input	UniProt Id
ATP5MC1	P05496, Q06055

2. Cristae formation (R-HSA-8949613)



Cristae are invaginations of the inner mitochondrial membrane that extend into the matrix and are lined with cytochrome complexes and F1Fo ATP synthase complexes. Cristae increase the surface area of the inner membranes allowing greater numbers of respiratory complexes. Cristae are also believed to serve as "proton pockets" to generate localized regions of higher membrane potential. The steps in the biogenesis of cristae are not yet completely elucidated (reviewed in Zick et al. 2009) but the formation of the Mitochondrial Contact Site and Cristae Organizing System (MICOS, formerly also known as MINOS, reviewed in Rampelt et al. 2016, Kozjak-Pavlovic 2016, van der Laan et al. 2016) and localized concentrations of cardiolipin are known to define the inward curvature of the inner membrane at the bases of cristae. MICOS also links these regions of the inner membrane with complexes (the SAM complex and, in fungi, the TOM complex) embedded in the outer membrane. CHCHD3 (MIC19) and IMMT (MIC60) subunits of MICOS also interact with OPA1 at the inner membrane (Darshi et al. 2011, Glytsou et al. 2016).

Formation of dimers or oligomers of the F1Fo ATP synthase complex causes extreme curvature of the inner membrane at the apices of cristae (reviewed in Seelert and Dencher 2011, Habersetzer et al. 2013). Defects in either MICOS or F1Fo ATP synthase oligomerization produce abnormal mitochondrial morphologies.

References

- Kozjak-Pavlovic V (2016). The MICOS complex of human mitochondria. *Cell Tissue Res.*. [🔗](#)
- Paumard P, Dautant A, Giraud MF, Ziani W, Larrieu I, Stines-Chaumeil C, ... Habersetzer J (2013). ATP synthase oligomerization: from the enzyme models to the mitochondrial morphology. *Int. J. Biochem. Cell Biol.*, 45, 99-105. [🔗](#)

Zerbes RM, van der Laan M, Pfanner N & Rampelt H (2016). Role of the mitochondrial contact site and cristae organizing system in membrane architecture and dynamics. *Biochim. Biophys. Acta*. [\[CrossRef\]](#)

Taylor SS, Ellisman MH, Perkins GA, Murphy AN, Koller A, Darshi M, ... Mendiola VL (2011). ChChd3, an inner mitochondrial membrane protein, is essential for maintaining crista integrity and mitochondrial function. *J. Biol. Chem.*, 286, 2918-32. [\[CrossRef\]](#)

Rabl R, Zick M & Reichert AS (2009). Cristae formation-linking ultrastructure and function of mitochondria. *Biochim. Biophys. Acta*, 1793, 5-19. [\[CrossRef\]](#)

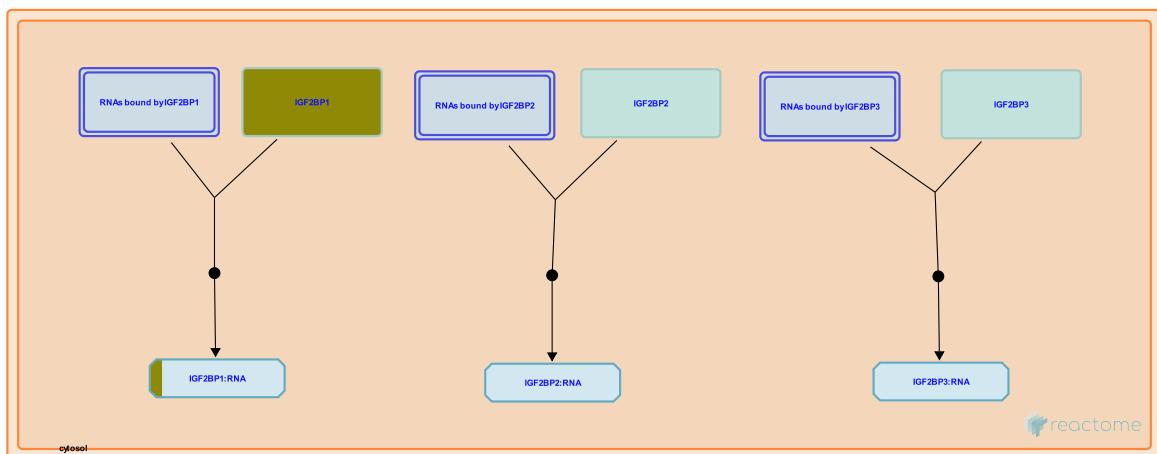
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Date	Action	Author
2016-11-26	Edited	May B
2016-11-26	Authored	May B
2016-11-27	Created	May B
2017-01-12	Reviewed	Harper JW
2017-02-05	Reviewed	Kozjak-Pavlovic V
2022-11-19	Modified	Wright A

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

Input	UniProt Id
ATP5MC1	P05496, Q06055

3. Insulin-like Growth Factor-2 mRNA Binding Proteins (IGF2BPs/IMPs/VICKZs) bind RNA ([R-HSA-428359](#))



Cellular compartments: cytosol.

Insulin-like Growth Factor-2 mRNA Binding Proteins (IGF2BPs) bind specific sets of RNA and regulate their translation, stability, and subcellular localization. IGF2BP1, IGF2BP2, and IGF2BP3 bind about 8400 protein-coding transcripts. The target RNAs contain the sequence motif CAUH (where H is A, U, or, C) and binding of IGFBPs increases the stability of the target RNAs.

References

- Nielsen J, Wewer UM, Christiansen J, Johnsen AH, Lykke-Andersen J & Nielsen FC (1999). A family of insulin-like growth factor II mRNA-binding proteins represses translation in late development. *Mol Cell Biol*, 19, 1262-70. [🔗](#)
- Nielsen J, Christiansen J & Nielsen FC (2001). A family of IGF-II mRNA binding proteins (IMP) involved in RNA trafficking. *Scand J Clin Lab Invest Suppl*, 234, 93-9. [🔗](#)
- Yisraeli JK (2005). VICKZ proteins: a multi-talented family of regulatory RNA-binding proteins. *Biol Cell*, 97, 87-96. [🔗](#)
- Rubinstein AM, Maizels Y, Oberman F, Rand K & Yisraeli JK (2007). VICKZ proteins mediate cell migration via their RNA binding activity. *RNA*, 13, 1558-69. [🔗](#)
- Wewer UM, Hansen TV, Christiansen J, Borup R, Jønson L, Vikesaa J & Nielsen FC (2006). RNA-binding IMPs promote cell adhesion and invadopodia formation. *EMBO J*, 25, 1456-68. [🔗](#)

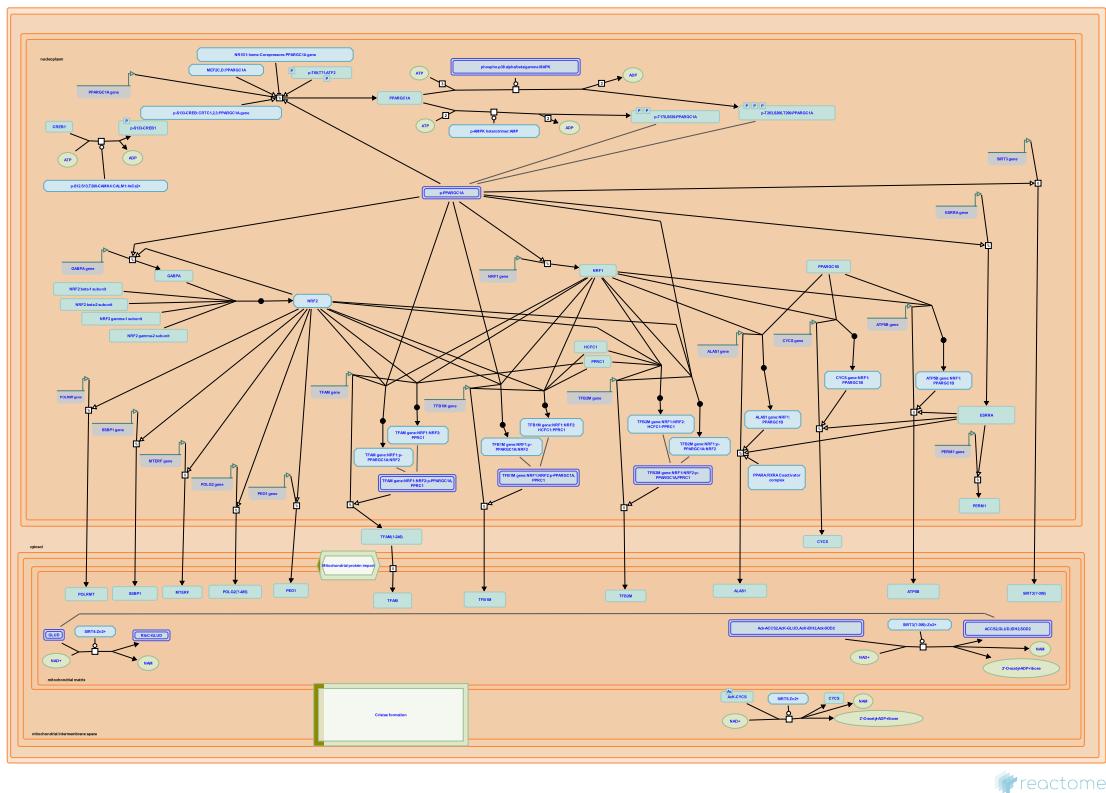
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2009-07-05	Edited	May B
2009-07-05	Authored	May B
2009-07-05	Created	May B
2010-05-30	Reviewed	Chao JA, Singer RH
2016-12-29	Modified	D'Eustachio P

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

Input	UniProt Id
IGF2BP1	Q9NZI8

4. Mitochondrial biogenesis (R-HSA-1592230)



Cellular compartments: nucleoplasm, mitochondrial matrix, cytosol.

Mitochondrial biogenesis and remodeling occur in response to exercise and redox state (reviewed in Scarpulla et al. 2012, Handy and Loscalzo 2012, Piantadosi and Suliman 2012, Scarpulla 2011, Wenz et al. 2011, Bo et al. 2010, Jornayvaz and Shulman 2010, Ljubicic et al. 2010, Hock and Kralli 2009, Canto and Auwerx 2009, Lin 2009, Scarpulla 2008, Ventura-Clapier et al. 2008). It is hypothesized that calcium influx and energy depletion are the signals that initiate changes in gene expression leading to new mitochondrial proteins. Energy depletion causes a reduction in ATP and an increase in AMP which activates AMPK. AMPK in turn phosphorylates the coactivator PGC-1alpha (PPARGC1A), one of the master regulators of mitochondrial biosynthesis. Likewise, p38 MAPK is activated by muscle contraction (possibly via calcium and CaMKII) and phosphorylates PGC-1alpha. CaMKIV responds to intracellular calcium by phosphorylating CREB, which activates expression of PGC-1alpha.

Deacetylation of PGC-1alpha by SIRT1 may also play a role in activation (Canto et al. 2009, Gurd et al. 2011), however Sirt11 deacetylation of Ppargc1a in mouse impacted genes related to glucose metabolism rather than mitochondrial biogenesis (Rodgers et al. 2005) and mice lacking SIRT1 in muscle had normal levels of mitochondrial biogenesis in response to exercise (Philp et al. 2011) so the role of deacetylation is not fully defined. PGC-1beta and PPRC appear to act similarly to PGC-1alpha but they have not been as well studied.

Phosphorylated PGC-1alpha does not bind DNA directly but instead interacts with other transcription factors, notably NRF1 and NRF2 (via HCF1). NRF1 and NRF2 together with PGC-1alpha activate the transcription of nuclear-encoded, mitochondrially targeted proteins such as TFB2M, TFB1M, and TFAM.

References

Veksler V, Garnier A & Ventura-Clapier R (2008). Transcriptional control of mitochondrial biogenesis: the central role of PGC-1alpha. *Cardiovasc. Res.*, 79, 208-17. [🔗](#)

Lin JD (2009). Minireview: the PGC-1 coactivator networks: chromatin-remodeling and mitochondrial energy metabolism. *Mol. Endocrinol.*, 23, 2-10. [🔗](#)

Scarpulla RC (2011). Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. *Biochim Biophys Acta*, 1813, 1269-78. [🔗](#)

Jornayvaz FR & Shulman GI (2010). Regulation of mitochondrial biogenesis. *Essays Biochem.*, 47, 69-84. [🔗](#)

Holloway GP, Spriet L, Bonen A, Heigenhauser GJ, Moyes CD, Gurd BJ, ... Yoshida Y (2011). Nuclear SIRT1 activity, but not protein content, regulates mitochondrial biogenesis in rat and human skeletal muscle. *Am J Physiol Regul Integr Comp Physiol*, 301, R67-75. [🔗](#)

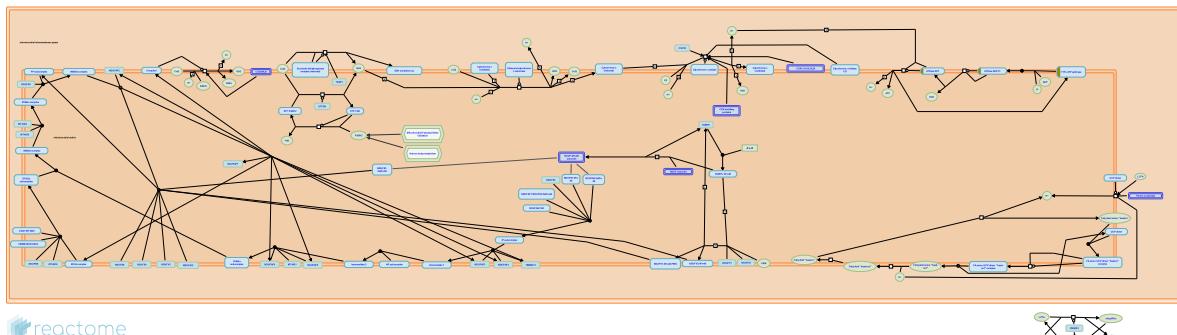
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2011-08-20	Edited	May B
2011-08-20	Authored	May B
2011-09-09	Created	May B
2013-12-07	Reviewed	Lezza AM
2022-11-19	Modified	Wright A

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

Input	UniProt Id
ATP5MC1	P05496, Q06055

5. Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins. (R-HSA-163200)



Oxidation of fatty acids and pyruvate in the mitochondrial matrix yield large amounts of NADH. The respiratory electron transport chain couples the re-oxidation of this NADH to NAD⁺ to the export of protons from the mitochondrial matrix, generating a chemiosmotic gradient across the inner mitochondrial membrane. This gradient is used to drive the synthesis of ATP; it can also be bypassed by uncoupling proteins to generate heat, a reaction in brown fat that may be important in regulation of body temperature in newborn children.

References

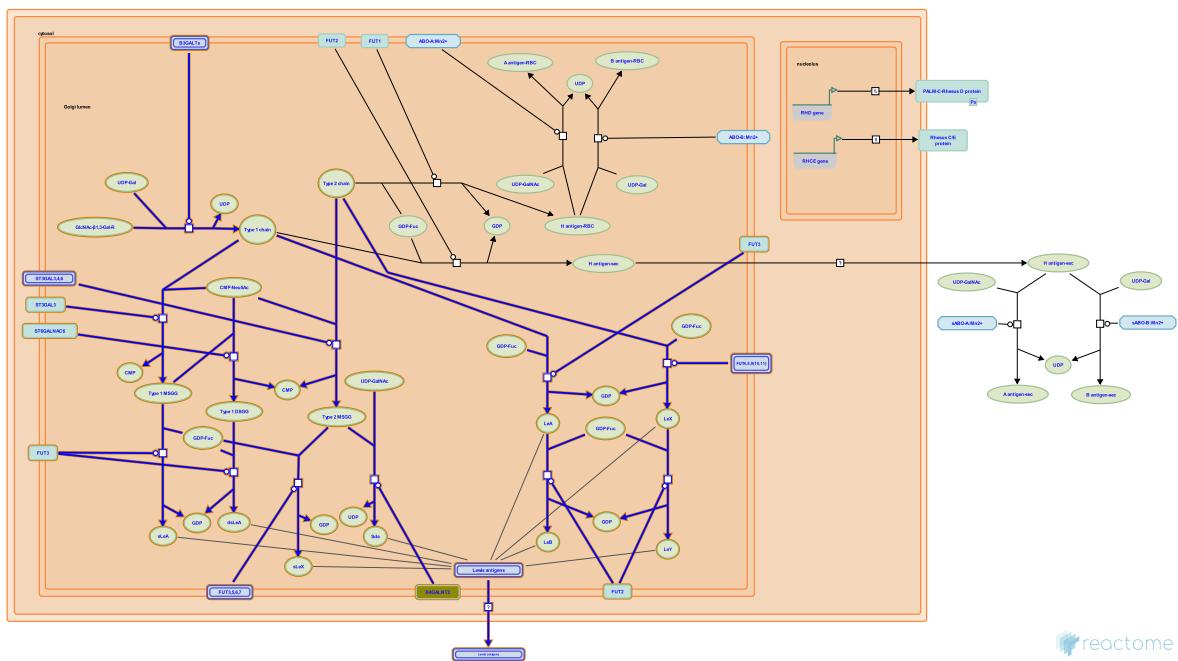
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2005-04-21	Created	Jassal B
2005-05-12	Reviewed	Ferguson SJ
2022-11-19	Modified	Wright A

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

Input	UniProt Id
ATP5MC1	P05496, Q06055

6. Lewis blood group biosynthesis (R-HSA-9037629)



The Lewis antigen system is a human blood group system based upon genes on chromosome 19 p13.3 (the *FUT3* gene aka the *Le* gene) and 19q13.3, (*FUT2* gene aka the *Se* gene). Both genes are expressed in glandular epithelia and have dominant alleles (Le and Se, respectively) coding for enzymes with fucosyltransferase activity and recessive alleles (le and se, respectively) that are non-functional. There are two main Lewis antigens, Lewis A and Lewis B which can result in three common phenotypes: Le(A+B-), Le(A+B+) and Le(A-B-). Lewis antigens are components of exocrine epithelial secretions, and can be adsorbed onto the surfaces of red blood cells (RBCs), therefore are not produced directly by RBCs themselves (Ewald & Sumner 2016).

The same two oligosaccharides (Type 1 and Type 2) used to determine ABO blood types are also utilised by the Lewis system. Fucosyltransferase 3 (*FUT3*, Le) adds fucose to Type 1 chains to form the Lewis A antigen (LeA). If the individual is a non-secretor (lacks the *Se* gene, homozygous *sese*), LeA is adsorbed onto the red cell, and that individual is LeA type. Approximately 80% of the population has the *Se* gene. Functional fucosyltransferase 2 (*FUT2*, Se) adds a fucose to LeA to form LeB. Both LeA and LeB present in the plasma of secretors but LeA preferentially adsorbs onto the RBC and therefore, the individual types as LeB. Other FUTs, especially *FUT4*, can add a fucose to Type 2 chains to form the Lewis X antigen (LeX). Further fucosylation of LeX by *FUT2* produces the Lewis Y antigen (LeY). LeX and LeY are structural isomers of LeA and LeB. The formation of LeY is controlled by *Se/se* as in the case for LeB. LeA and LeX antigens can also undergo sialylation to produce sialated forms of these antigens.

Aberrant glycosylation of tumour cells is recognised as a feature of cancer pathogenesis. Overexpression of fucosylated and sialated Lewis antigens frequently occurs on the surfaces of cancer cells and is mainly attributed to upregulated expression of the relevant fucosyltransferases (FUTs). The sialyl-Lewis A antigen (sLeA), also known as the CA19-9 antigen, is the most common tumour marker used primarily in the management of pancreatic and gastrointestinal cancers worldwide (Magnani 2004, Blanas et al. 2018).

Selectins (L-, E- and P-selectin) are type I membrane proteins composed of long N-terminus C-type lectin domains protruding into the extracellular space and with a short cytoplasmic tail. They bind carbohydrate structures through a Ca²⁺-dependent domain, the minimal sugar structure recognised fulfilled by sLeA and sLeX. Selectins are found on endothelial cells, platelets and leukocytes and are involved in trafficking of cells of the innate immune system, T lymphocytes and platelets, thereby playing important roles in chronic and acute inflammation and haemostasis. Selectins also play a role in cancer progression. Metastasis is facilitated by cell-cell interactions between cancer cells and endothelial cells in distant tissues. In addition, cancer cell interactions with platelets and leukocytes contribute to cancer cell adhesion, extravasation, and the establishment of metastatic lesions. Targeting selectins and their ligands as well as the enzymes involved in their generation, in particular sialyl transferases, could be a useful strategy in cancer treatment (Ley 2003, Laubli & Borsig 2010, Cheung et al. 2011, Natoli et al. 2016, Trinchera et al. 2017).

References

- Ewald DR & Sumner SC (2016). Blood type biochemistry and human disease. Wiley Interdiscip Rev Syst Biol Med, 8, 517-535. [🔗](#)
- Magnani JL (2004). The discovery, biology, and drug development of sialyl Lea and sialyl Lex. Arch. Biochem. Biophys., 426, 122-31. [🔗](#)
- Van Vliet SJ, van Kooyk Y, Sahasrabudhe NM, Blanas A & Rodríguez E (2018). Fucosylated Antigens in Cancer: An Alliance toward Tumor Progression, Metastasis, and Resistance to Chemotherapy. Front Oncol, 8, 39. [🔗](#)

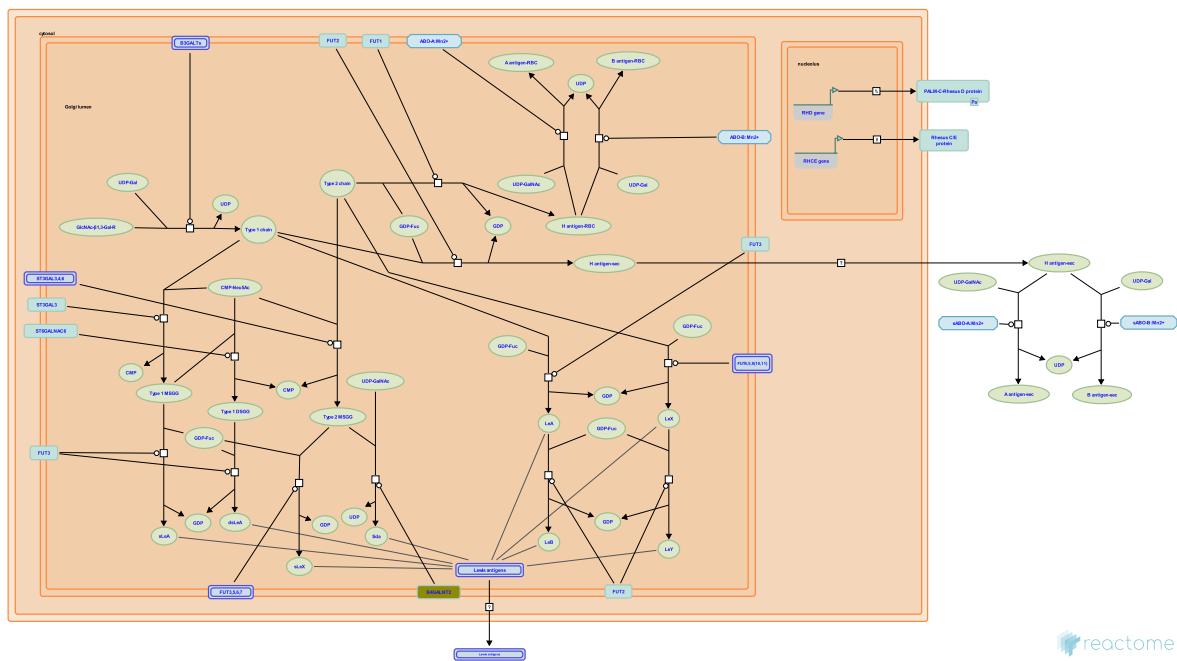
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2018-02-20	Created	Jassal B
2018-12-17	Reviewed	Matsui T
2022-11-19	Modified	Wright A

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

Input	UniProt Id
B4GALNT2	Q8NHY0

7. Blood group systems biosynthesis (R-HSA-9033658)



The association between blood type and disease has been studied since the beginning of the 20th Century (Anstee 2010, Ewald & Sumner 2016). Landsteiner's discovery of blood groups in 1900 was based on agglutination patterns of red blood cells when blood types from different donors were mixed (Landsteiner 1931, Owen 2000, Tan & Graham 2013). His work is the basis of routine compatibility testing and transfusion practices today. The immune system of patients receiving blood transfusions will attack any donor red blood cells that contain antigens that differ from their self-antigens. Therefore, matching blood types is essential for safe blood transfusions. Landsteiner's classification of the ABO blood groups confirmed that antigens were inherited characteristics. In the 1940s, it was established that the specificity of blood group antigens was determined by their unique oligosaccharide structures. Since then, exponential advances in technology have resulted in the identification of over 300 blood group antigens, classified into more than 35 blood group systems by the International Society of Blood Transfusion (ISBT) (Storry et al. 2016).

Blood group antigens comprise either a protein portion or oligosaccharide sequence attached on a glycolipid or glycoprotein. The addition of one or more specific sugar molecules to this oligosaccharide sequence at specific positions by a variety of glycosyltransferases results in the formation of mature blood group antigens. The genes that code for glycosyltransferases can contain genetic changes that produce antigenic differences, resulting in new antigens or loss of expression. Blood group antigens are found on red blood cells (RBCs), platelets, leukocytes, and plasma proteins and also exist in soluble form in bodily secretions such as breast milk, seminal fluid, saliva, sweat, gastric secretions and urine. Blood groups are implicated in many diseases such as those related to malignancy (Rummel & Ellsworth 2016), the cardiovascular system (Liumbruno & Franchini 2013), metabolism (Meo et al. 2016, Ewald & Sumner 2016) and infection (Rios & Bianco 2000, McCullough 2014). The most important and best-studied blood groups are the ABO, Lewis and Rhesus systems. The biosynthesis of the antigens in these systems is described in this section.

References

- Ewald DR & Sumner SC (2016). Blood type biochemistry and human disease. Wiley Interdiscip Rev Syst Biol Med, 8, 517-535. [View](#)

Ellsworth RE & Rummel SK (2016). The role of the histoblood ABO group in cancer. Future Sci OA, 2 , FSO107. [🔗](#)

Flegel WA, Moulds JM, van der Schoot CE, Daniels G, Storry JR, Nogues N, ... Peyrard T (2016). International society of blood transfusion working party on red cell immunogenetics and terminology: report of the Seoul and London meetings. ISBT Sci Ser, 11, 118-122. [🔗](#)

Landsteiner K (1931). INDIVIDUAL DIFFERENCES IN HUMAN BLOOD. Science, 73, 403-9. [🔗](#)

Owen R (2000). Karl Landsteiner and the first human marker locus. Genetics, 155, 995-8. [🔗](#)

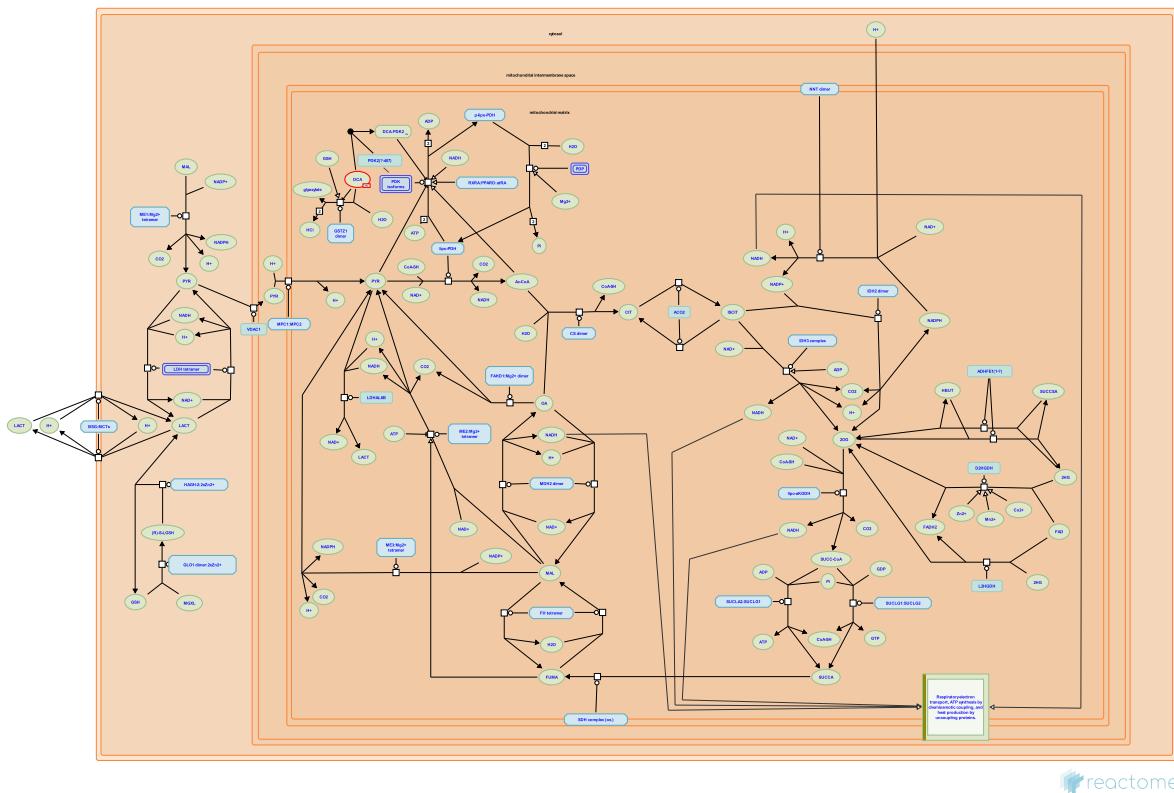
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2017-12-27	Created	Jassal B
2018-12-17	Reviewed	Matsui T
2022-11-19	Modified	Wright A

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

Input	UniProt Id
B4GALNT2	Q8NHY0

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



reactome

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

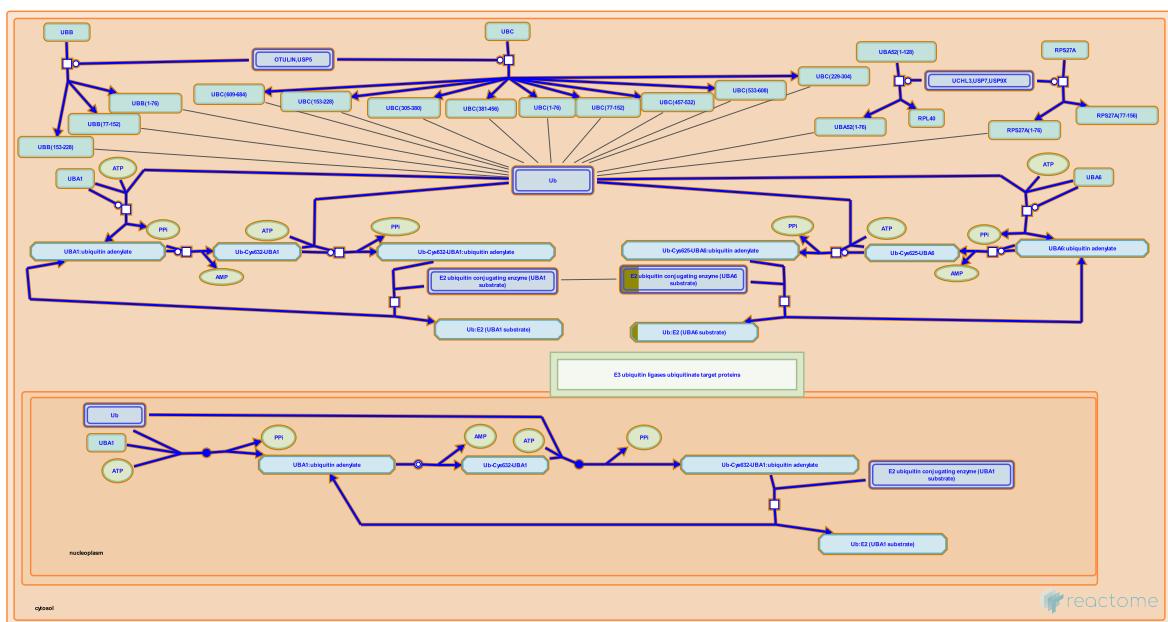
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2003-11-03	Authored	Birney E, Schmidt EE, D'Eustachio P
2011-07-07	Edited	Jassal B
2011-07-07	Created	Jassal B
2022-11-19	Modified	Wright A

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

Input	UniProt Id
ATP5MC1	P05496, Q06055

9. Synthesis of active ubiquitin: roles of E1 and E2 enzymes (R-HSA-8866652)



Ubiquitin monomers are processed from larger precursors and then activated by formation of a thiol ester bond between ubiquitin and a cysteine residue of an E1 activating enzyme (UBA1 or UBA6, Jin et al. 2007). The ubiquitin is then transferred to the active site cysteine residue of an E2 conjugating enzyme (reviewed in van Wijk and Timmers 2010, Kleiger and Mayor 2014, Stewart et al. 2016). Precursor proteins containing multiple ubiquitin monomers (polyubiquitins) are produced from the UBB and UBC genes. Precursors containing a single ubiquitin fused to a ribosomal protein are produced from the UBA52 and RPS27A genes. The proteases OTULIN and USP5 are very active in polyubiquitin processing, whereas the proteases UCHL3, USP7, and USP9X cleave the ubiquitin-ribosomal protein precursors yielding ubiquitin monomers (Grou et al. 2015). Other enzymes may also process ubiquitin precursors. A resultant ubiquitin monomer is activated by adenylation of its C-terminal glycine followed by conjugation of the C-terminus to a cysteine residue of the E1 enzymes UBA1 or UBA6 via a thiol ester bond (Jin et al. 2007, inferred from rabbit homologues in Haas et al. 1982, Hershko et al. 1983). The ubiquitin is then transferred from the E1 enzyme to a cysteine residue of one of several E2 enzymes (reviewed in van Wijk and Timmers 2010, Stewart et al. 2016).

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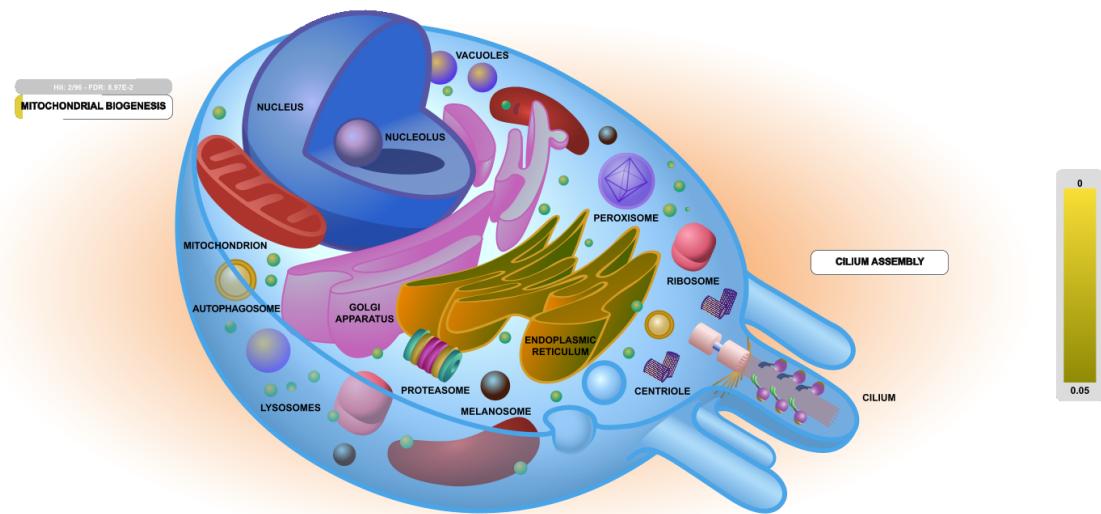
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2016-04-02	Created	May B
2016-08-11	Reviewed	Azevedo JE
2022-11-23	Modified	Wright A

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

Input	UniProt Id
UBE2Z	Q9H832

10. Organelle biogenesis and maintenance (R-HSA-1852241)



This module describes the biogenesis of organelles. Organelles are subcellular structures of distinctive morphology and function. The organelles of human cells include: mitochondria, endoplasmic reticulum, Golgi apparatus, vacuoles, nucleus, (auto)phagosome, centriole, lysosome, melanosome, myofibril, nucleolus, peroxisome, cilia (in some cell types), proteasome, ribosome, and transport vesicles.

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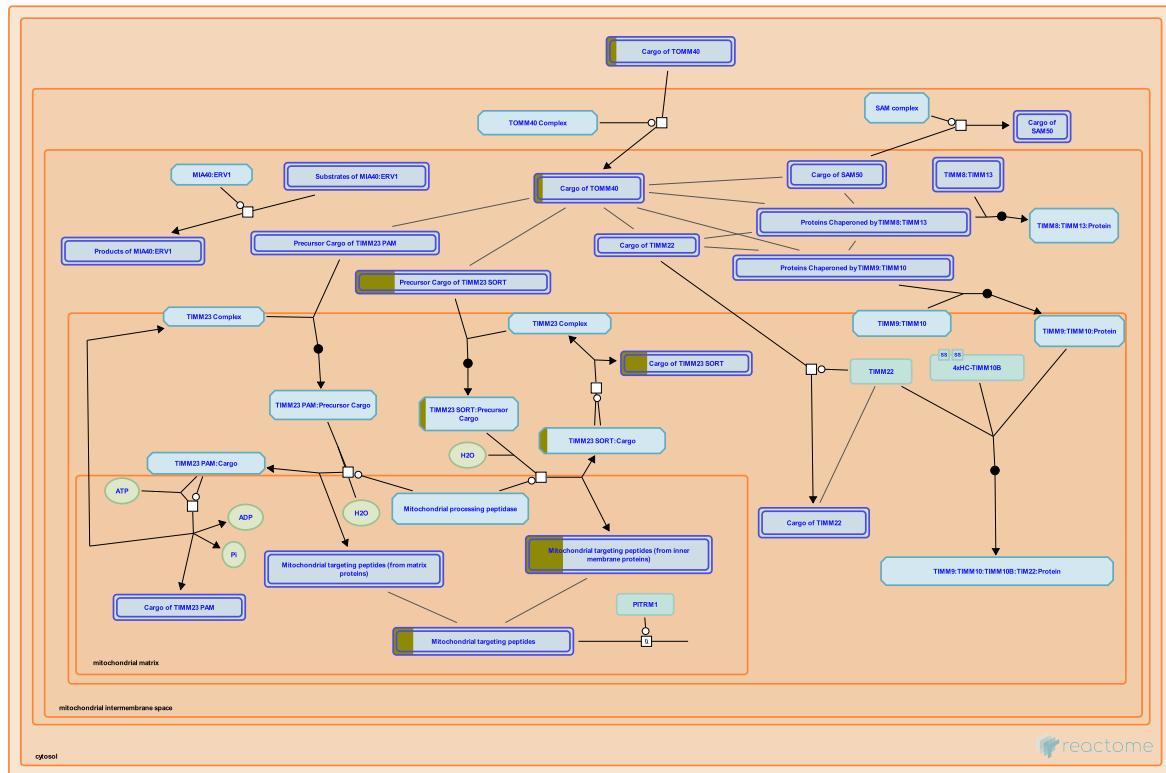
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2011-10-28	Reviewed	Matthews L
2011-10-28	Authored	Matthews L
2011-10-28	Created	Matthews L
2022-11-19	Modified	Wright A

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

Input	UniProt Id
ATP5MC1	P05496, Q06055

11. Mitochondrial protein import (R-HSA-1268020)



Cellular compartments: mitochondrial outer membrane, cytosol, mitochondrial matrix, mitochondrial intermembrane space, mitochondrial inner membrane.

A human mitochondrion contains about 1500 proteins, more than 99% of which are encoded in the nucleus, synthesized in the cytosol and imported into the mitochondrion. Proteins are targeted to four locations (outer membrane, intermembrane space, inner membrane, and matrix) and must be sorted accordingly (reviewed in Kutik et al. 2007, Milenkovic et al. 2007, Bolender et al. 2008, Endo and Yamano 2009, Wiedemann and Pfanner 2017, Kang et al. 2018). Newly synthesized proteins are transported from the cytosol across the outer membrane by the TOMM40:TOMM70 complex. Proteins that contain presequences first interact with the TOMM20 subunit of the complex while proteins that contain internal targeting elements first interact with the TOMM70 subunit. After initial interaction the protein is conducted across the outer membrane by TOMM40 subunits. In yeast some proteins such as Aco1, Atp1, Cit1, Idh1, and Atp2 have both presequences that interact with TOM20 and mature regions that interact with TOM70 (Yamamoto et al. 2009).

After passage across the outer membrane, proteins may be targeted to the outer membrane via the SAMM50 complex, to the inner membrane via the TIMM22 or TIMM23 complexes (reviewed in van der Laan et al. 2010), to the matrix via the TIMM23 complex (reviewed in van der Laan et al. 2010), or proteins may fold and remain in the intermembrane space (reviewed in Stojanovski et al. 2008, Deponte and Hell 2009, Sideris and Tokatlidis 2010). Presequences on matrix and inner membrane proteins cause interaction with TIMM23 complexes; internal targeting sequences cause outer membrane proteins to interact with the SAMM50 complex and inner membrane proteins to interact with the TIMM22 complex. While in the intermembrane space hydrophobic proteins are chaperoned by the TIMM8:TIMM13 complex and/or the TIMM9:TIMM10:FXC1 complex.

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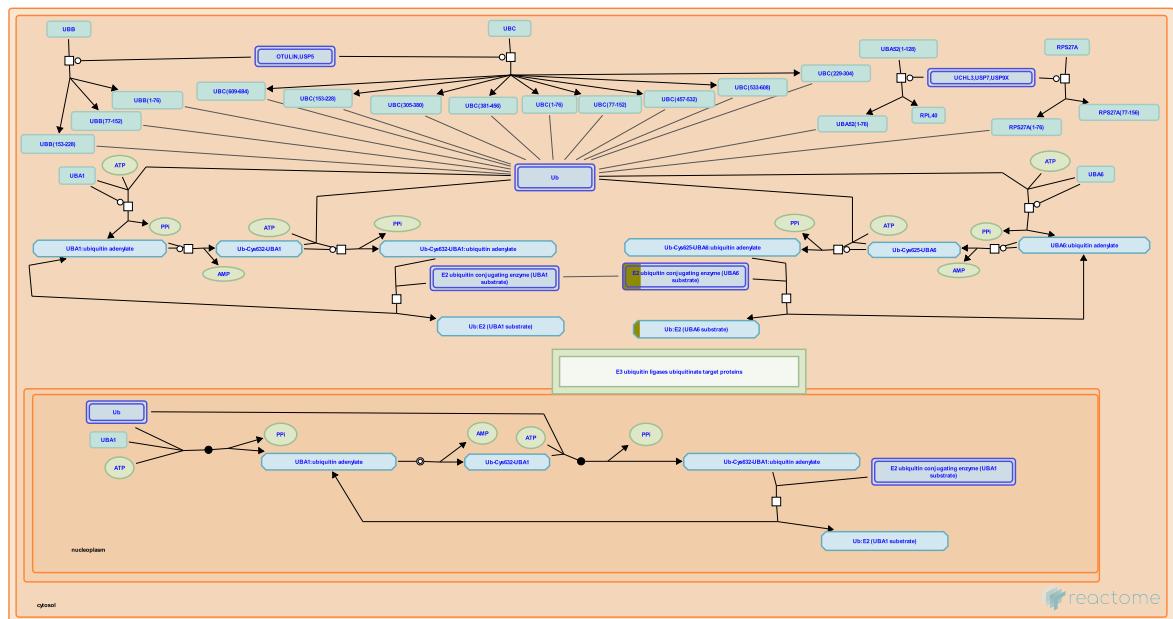
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2011-05-09	Created	May B
2011-11-02	Reviewed	D'Eustachio P
2012-02-12	Reviewed	Endo T
2022-11-19	Modified	Wright A

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

Input	UniProt Id
ATP5MC1	P05496

12. Protein ubiquitination (R-HSA-8852135)



Ubiquitin is a small, 76 amino acid residue protein that is conjugated by E3 ubiquitin ligases to other proteins in order to regulate their function or degradation (enzymatic cascade reviewed in Neutzner and Neutzner 2012, Kleiger and Mayor 2014, structures and mechanisms of conjugating enzymes reviewed in Lorenz et al. 2013). Ubiquitination of target proteins usually occurs between the C-terminal glycine residue of ubiquitin and a lysine residue of the target, although linkages with cysteine, serine, and threonine residues are also observed (reviewed in Wang et al. 2012, McDowell and Philpott 2013).

Ubiquitin must first be processed from larger precursors and then activated by formation of a thiol ester bond between ubiquitin and an E1 activating enzyme (UBA1 or UBA6) and transfer to an E2 conjugating enzyme before being transferred by an E3 ligase to a target protein. Precursor proteins containing multiple ubiquitin monomers (polyubiquitins) are produced from the UBB and UBC genes; precursors containing a single ubiquitin monomer and a ribosomal protein are produced from the UBA52 and RPS27A genes. Many proteases (deubiquitinases) may potentially process these precursors yielding monomeric ubiquitin. The proteases OTULIN and USP5 are particularly active in cleaving the polyubiquitin precursors, whereas the proteases UCHL3, USP7, and USP9X cleave the ubiquitin-ribosomal protein precursors yielding ubiquitin monomers (Grou et al. 2015). A resultant ubiquitin monomer is activated by adenylation of the C-terminal glycine followed by conjugation of the C-terminus to a cysteine residue of the E1 enzymes UBA1 or UBA6 via a thiol ester bond. The ubiquitin is then transferred from the E1 enzyme to a cysteine residue of one of several E2 enzymes (reviewed in van Wijk and Timmers 2010, Stewart et al. 2016). Through a less well characterized mechanism, E3 ubiquitin ligases then bring a target protein and the E2-ubiquitin conjugate into proximity so that the ubiquitin is transferred via formation of an amide bond to a particular lysine residue (or, in rarer cases, a thiol ester bond to a cysteine residue or an ester bond to a serine or threonine residue) of the target protein (reviewed in Berndsen and Wolberger 2014). Based on protein homologies, families of E3 ubiquitin ligases have been identified that include RING-type ligases (reviewed in Deshaies et al. 2009, Metzger et al. 2012, Metzger et al. 2014), HECT-type ligases (reviewed in Rotin et al. 2009, Metzger et al. 2012), and RBR-type ligases (reviewed in Dove et al. 2016). A subset of the RING-type ligases participate in CULLIN-RING ligase complexes (CRLs which include SCF complexes, reviewed in Lee and Zhou 2007, Genschik et al. 2013, Skaar et al. 2013, Lee et al. 2014).

Some E3-E2 combinations catalyze mono-ubiquitination of the target protein (reviewed in Nakagawa and Nakayama 2015). Other E3-E2 combinations catalyze conjugation of further ubiquitin monomers to the initial ubiquitin, forming polyubiquitin chains. (It may also be possible for some E3-E2 combinations to preassemble polyubiquitin and transfer it as a unit to the target protein.) Ubiquitin contains several lysine (K) residues and a free alpha amino group to which further ubiquitin can be conjugated. Thus different types of polyubiquitin are possible: K11 linked polyubiquitin is observed in endoplasmic reticulum-associated degradation (ERAD), K29 linked polyubiquitin is observed in lysosomal degradation, K48 linked polyubiquitin directs target proteins to the proteasome for degradation, whereas K63 linked polyubiquitin generally acts as a scaffold to recruit other proteins in several cellular processes, notably DNA repair (reviewed in Komander et al. 2009). Ubiquitination is highly regulated (reviewed in Vittal et al. 2015) and affects all cellular processes including DNA damage response (reviewed in Brown and Jackson 2015), immune signaling (reviewed in Park et al. 2014, Lutz-Nicoladoni et al. 2015), and regulation of normal and cancerous cell growth (reviewed in Skaar and Pagano 2009, Yerlikaya and Yontem 2013, Strikoudis et al. 2014).

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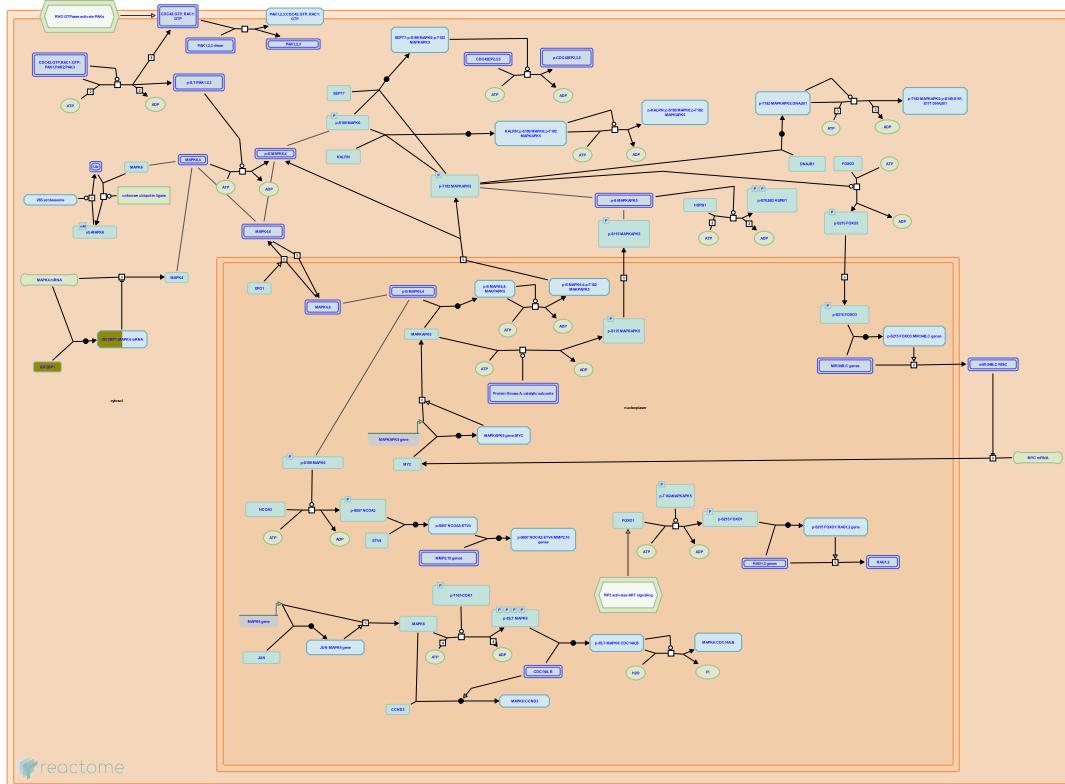
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2016-01-13	Created	May B
2016-08-11	Reviewed	Azevedo JE
2022-11-19	Modified	Wright A

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

Input	UniProt Id
UBE2Z	Q9H832

13. MAPK6/MAPK4 signaling (R-HSA-5687128)



MAPK6 and MAPK4 (also known as ERK3 and ERK4) are vertebrate-specific atypical MAP kinases. Atypical MAPK are less well characterized than their conventional counterparts, and are generally classified as such based on their lack of activation by MAPKK family members. Unlike the conventional MAPK proteins, which contain a Thr-X-Tyr motif in the activation loop, MAPK6 and 4 have a single Ser-Glu-Gly phospho-acceptor motif (reviewed in Coulombe and Meloche, 2007; Cagnello et al, 2011). MAPK6 is also distinct in being an unstable kinase, whose turnover is mediated by ubiquitin-dependent degradation (Coulombe et al, 2003; Coulombe et al, 2004). The biological functions and pathways governing MAPK6 and 4 are not well established. MAPK6 and 4 are phosphorylated downstream of class I p21 activated kinases (PAKs) in a RAC- or CDC42-dependent manner (Deleris et al, 2008; Perander et al, 2008; Deleris et al, 2011; De La Mota-Peynado et al, 2011). One of the only well established substrates of MAPK6 and 4 is MAPKAPK5, which contributes to cell motility by promoting the HSBP1-dependent rearrangement of F-actin (Gerits et al, 2007; Kostenko et al, 2009a; reviewed in Kostenko et al, 2011b). The atypical MAPKs also contribute to cell motility and invasiveness through the NCOA3:ETV4-dependent regulation of MMP gene expression (Long et al, 2012; Yan et al, 2008; Qin et al, 2008). Both of these pathways may be misregulated in human cancers (reviewed in Myant and Sansom, 2011; Kostenko et al, 2012).

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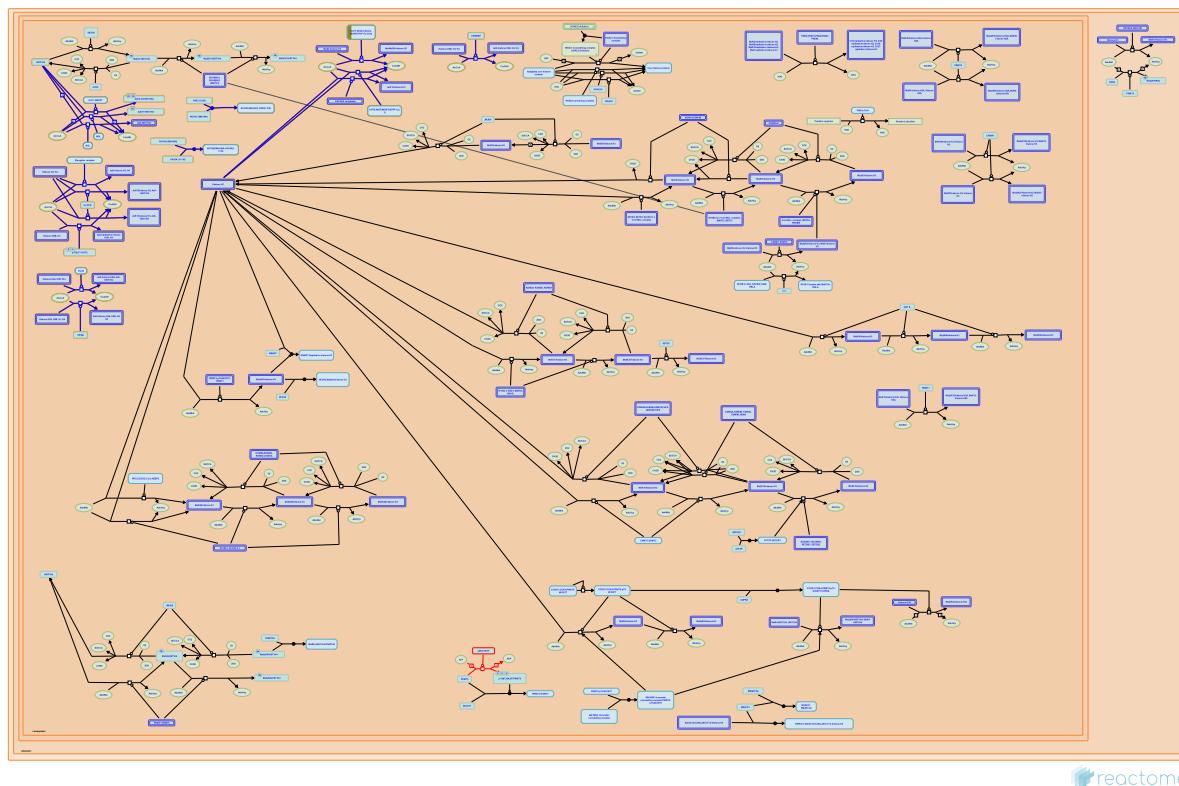
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2015-04-24	Reviewed	Moens U
2015-05-05	Reviewed	Seternes OM
2015-05-12	Reviewed	Mathien S, Soulez M, Meloche S
2015-05-13	Edited	Rothfels K
2022-11-19	Modified	Wright A

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

Input	UniProt Id
IGF2BP1	Q9NZI8

14. HATs acetylate histones ([R-HSA-3214847](#))



Histone acetyltransferases (HATs) involved in histone modifications are referred to as A-type or nuclear HATs. They can be grouped into at least four families based on sequence conservation within the HAT domain: Gcn5/PCAF, MYST, p300/CBP and Rtt109. The p300/CBP and Rtt109 families are specific to metazoans and fungi respectively (Marmorstein & Trievel 2009). Gcn5/PCAF and MYST family members have no significant sequence homology but share a globular alpha/beta fold with a common structure involved in acetyl-Coenzyme A (ACA) binding. Both use a conserved glutamate residue for the acetyl transfer reaction but may not share a common catalytic mechanism (Trievel et al. 1999, Tanner et al. 1999, Yan et al. 2002, Berndsen et al. 2007). The p300/CBP HAT domain has no homology with the other families but some structural conservation within the ACA-binding core (Liu et al. 2008). In addition to histone acetylation, members of all 3 human HAT families have been shown to acetylate non-histones (Glozak et al. 2005).

HATs and histone deacetylase (HDAC) enzymes generally act not alone but as part of multiprotein complexes. There are numerous examples in which subunits of HAT or HDAC complexes influence their substrate specificity and lysine preference, which in turn, affect the broader functions of these enzymes (Shahbazian & Grunstein 2007).

N.B. The coordinates of post-translational modifications represented and described here follow UniProt standard practice whereby coordinates refer to the translated protein before any further processing. Histone literature typically refers to coordinates of the protein after the initiating methionine has been removed. Therefore the coordinates of post-translated residues in the Reactome database and described here are frequently +1 when compared with the literature.

References

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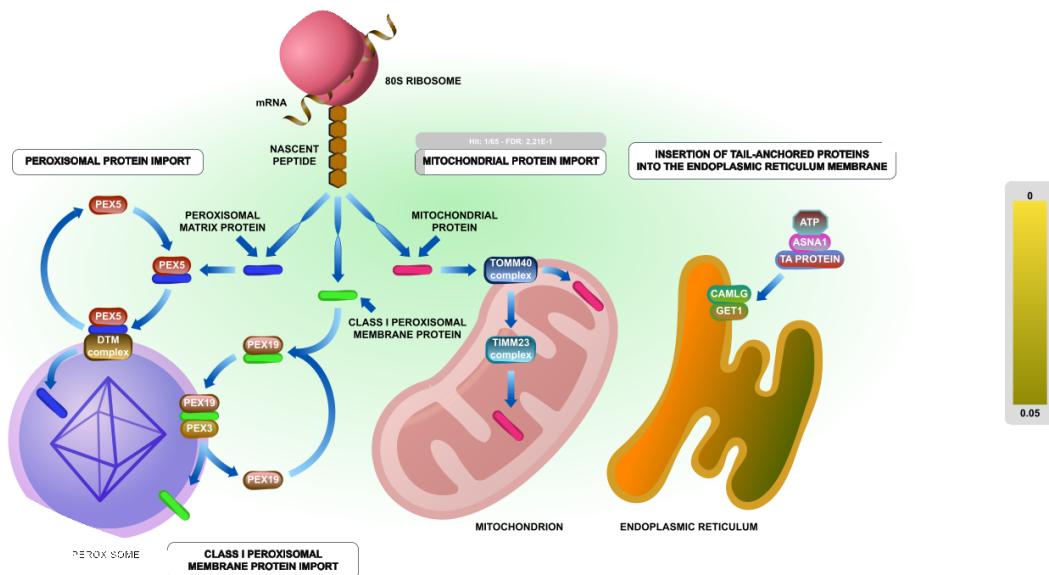
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2013-11-01	Edited	Jupe S
2013-11-18	Reviewed	Karagiannis T
2022-11-19	Modified	Wright A

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

Input	UniProt Id
KAT7	O95251

15. Protein localization (R-HSA-9609507)



Protein localization encompasses the processes that establish and maintain proteins at specific locations. Mechanisms that target proteins to particular locations in the cell typically involve a motif in the targeted protein that interacts with proteins located at the destination (reviewed in Bauer et al. 2015).

Mitochondrial proteins encoded in the nucleus may be targeted to the outer membrane, intermembrane space, inner membrane, or the matrix (reviewed in Kutik et al. 2007, Milenkovic et al. 2007, Bolender et al. 2008, Ender and Yamano 2009, Wiedemann and Pfanner 2017, Kang et al. 2018). A presequence or an internal targeting sequence causes a protein in the cytosol to interact with the TOMM40:TOMM70 complex in the outer mitochondrial membrane. After passage across the outer membrane, sequence motifs cause proteins to be targeted to the outer membrane via the SAMM50 complex, to the inner membrane via the TIMM22 or TIMM23 complexes, to the matrix via the TIMM23 complex, or proteins may fold and remain in the intermembrane space.

All of the proteins contained in the peroxisomal matrix are imported from the cytosol by a unique mechanism that does not require the imported proteins to be unfolded as they cross the membrane (reviewed in Ma et al. 2011, Fujiki et al. 2014, Francisco et al. 2017). In the cytosol, receptor proteins, PEX5 and PEX7, bind to specific sequence motifs in cargo proteins and then interact with a protein complex containing PEX13, PEX14, PEX2, PEX10, and PEX12 in the peroxisome membrane. The cargo proteins then pass through a proteinaceous channel in the membrane and PEX5 is recycled by a mechanism involving ubiquitination and deubiquitination.

Most peroxisomal membrane proteins (PMPs) are inserted into the peroxisomal membrane by the receptor-chaperone PEX19 and the docking receptor PEX3 (reviewed in Ma et al. 2011, Fujiki et al. 2014). PEX19 binds the PMP as it is translated in the cytosol. The PEX19:PMP complex then interacts with PEX3 located in the peroxisomal membrane. Through a mechanism that is not yet clear, the PMP is inserted into the peroxisomal membrane and PEX19 dissociates from PEX3.

References

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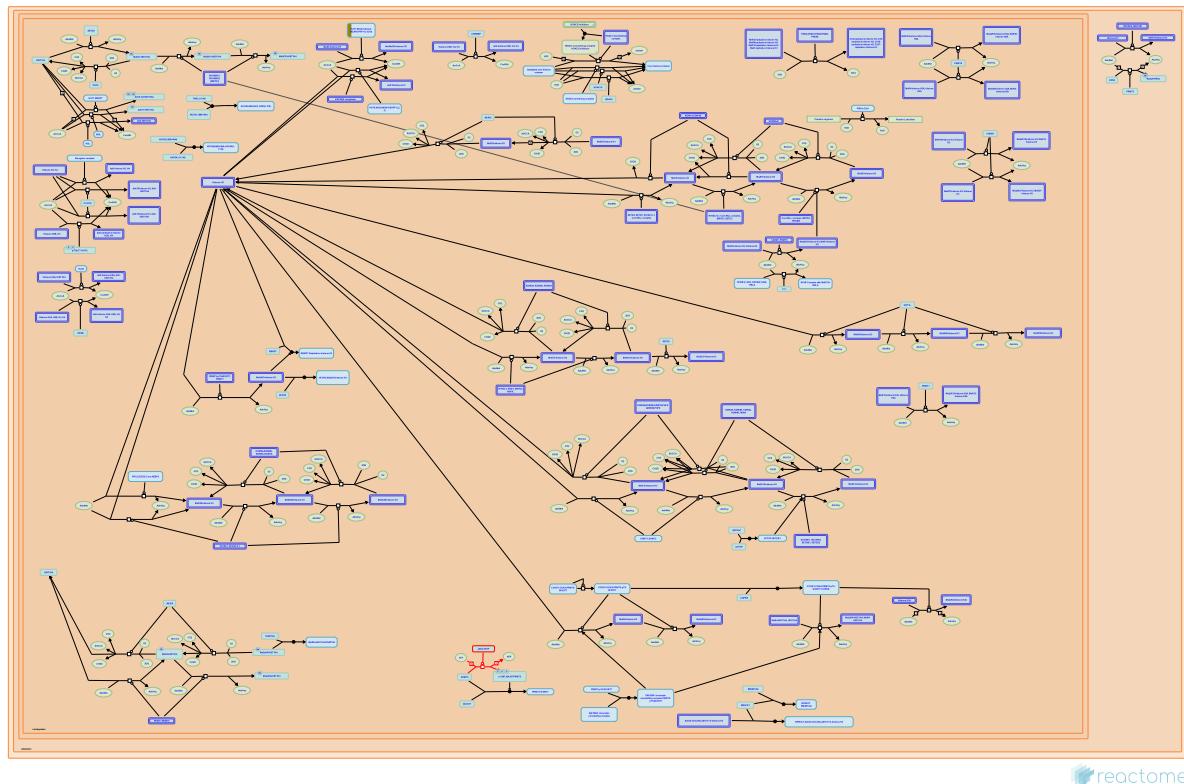
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2018-05-26	Authored	May B
2018-05-26	Created	May B
2022-11-19	Modified	Wright A

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

Input	UniProt Id
ATP5MC1	P05496

16. Chromatin organization (R-HSA-4839726)



Cellular compartments: nucleoplasm.

Chromatin organization refers to the composition and conformation of complexes between DNA, protein and RNA. It is determined by processes that result in the specification, formation or maintenance of the physical structure of eukaryotic chromatin. These processes include histone modification, DNA modification, and transcription. The modifications are bound by specific proteins that alter the conformation of chromatin.

References

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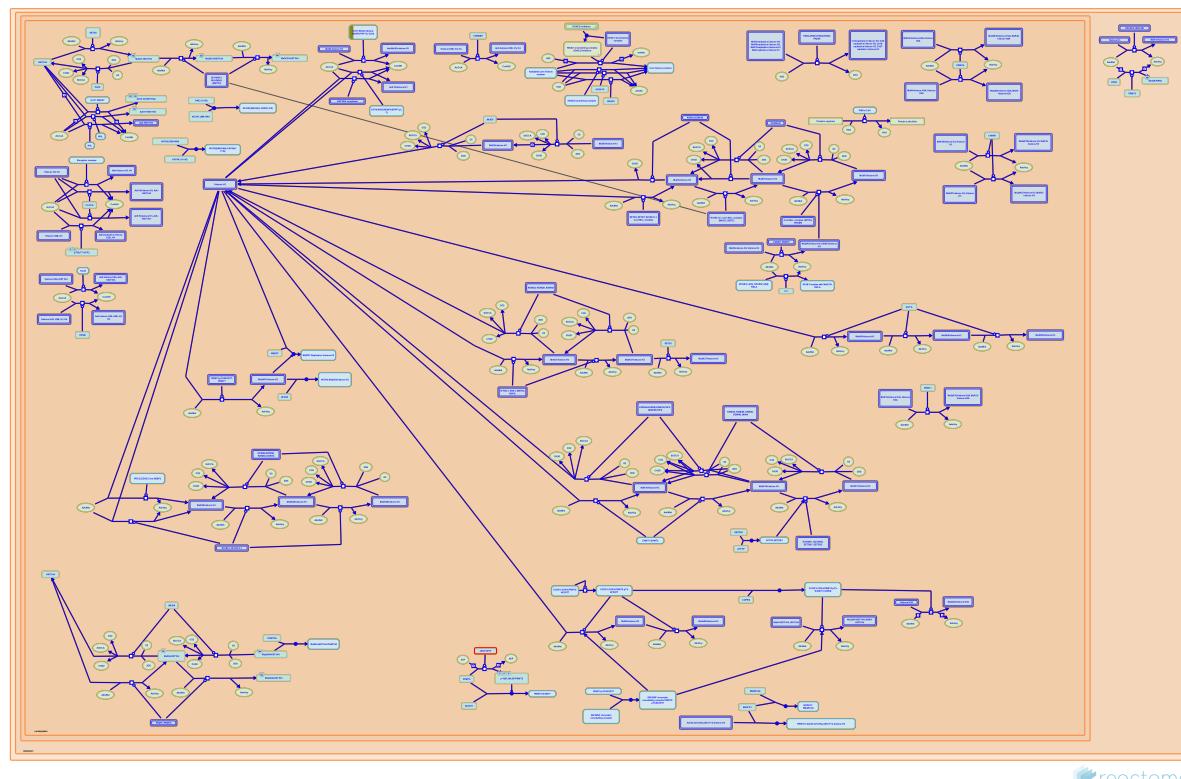
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2013-11-02	Authored	May B
2013-11-02	Created	May B
2013-11-18	Reviewed	Karagiannis T
2022-11-19	Modified	Wright A

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

Input	UniProt Id
KAT7	O95251

17. Chromatin modifying enzymes (R-HSA-3247509)



reactome

Eukaryotic DNA is associated with histone proteins and organized into a complex nucleoprotein structure called chromatin. This structure decreases the accessibility of DNA but also helps to protect it from damage. Access to DNA is achieved by highly regulated local chromatin decondensation.

The 'building block' of chromatin is the nucleosome. This contains ~150 bp of DNA wrapped around a histone octamer which consists of two each of the core histones H2A, H2B, H3 and H4 in a 1.65 left-handed superhelical turn (Luger et al. 1997, Andrews & Luger 2011).

Most organisms have multiple genes encoding the major histone proteins. The replication-dependent genes for the five histone proteins are clustered together in the genome in all metazoans. Human replication-dependent histones occur in a large cluster on chromosome 6 termed HIST1, a smaller cluster HIST2 on chromosome 1q21, and a third small cluster HIST3 on chromosome 1q42 (Marzluff et al. 2002). Histone genes are named systematically according to their cluster and location within the cluster.

The 'major' histone genes are expressed primarily during the S phase of the cell cycle and code for the bulk of cellular histones. Histone variants are usually present as single-copy genes that are not restricted in their expression to S phase, contain introns and are often polyadenylated (Old & Woodland 1984). Some variants have significant differences in primary sequence and distinct biophysical characteristics that are thought to alter the properties of nucleosomes. Others localize to specific regions of the genome. Some variants can exchange with pre-existing major histones during development and differentiation, referred to as replacement histones (Kamakaka & Biggins 2005). These variants can become the predominant species in differentiated cells (Pina & Suau 1987, Wunsch et al. 1991). Histone variants may have specialized functions in regulating chromatin dynamics.

The H2A histone family has the highest sequence divergence and largest number of variants. H2A.Z and H2A.XH2A are considered 'universal variants', found in almost all organisms (Talbert & Henikoff 2010). Variants differ mostly in the C-terminus, including the docking domain, implicated in interactions with the (H3-H4)x2 tetramer within the nucleosome, and in the L1 loop, which is the interaction interface of H2A-H2B dimers (Bonisch & Hake 2012). Canonical H2A proteins are expressed almost exclusively during S-phase. There are several nearly identical variants (Marzluff et al. 2002). No functional specialization of these canonical H2A isoforms has been demonstrated (Bonisch & Hake 2012). Reversible histone modifications such as acetylation and methylation regulate transcription from genomic DNA, defining the 'readability' of genes in specific tissues (Kouzarides 2007, Marmorstein & Trievel 2009, Butler et al. 2012).

N.B. The coordinates of post-translational modifications represented here follow Reactome standardized naming, which includes the UniProt standard practice whereby coordinates refer to the translated protein before any further processing. Histone literature typically refers to coordinates of the protein after the initiating methionine has been removed; therefore the coordinates of post-translated histone residues described here are frequently +1 when compared with the literature. For more information on Reactome's standards for naming pathway events, the molecules that participate in them and representation of post-translational modifications, please refer to Naming Conventions on the Reactome Wiki or Jupe et al. 2014.

References

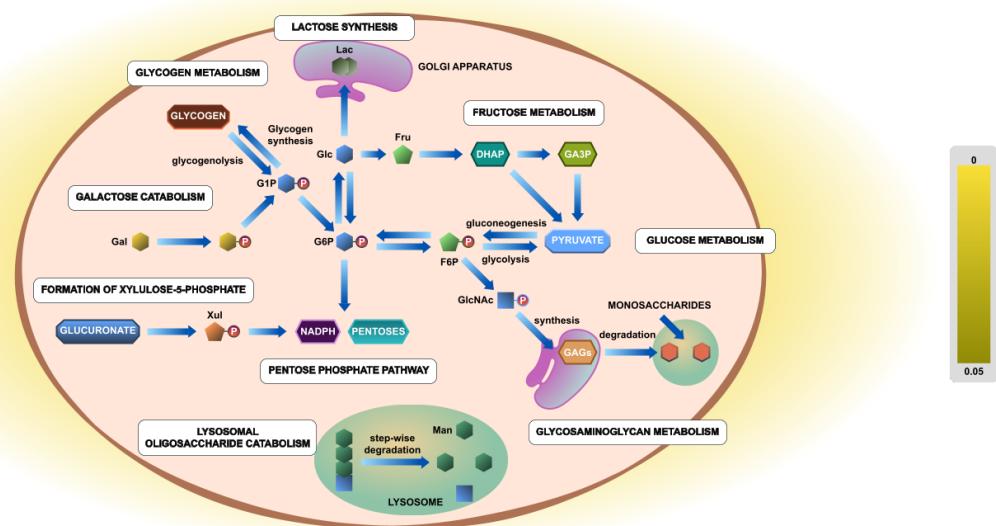
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2013-11-18	Edited	Jupe S
2013-11-18	Reviewed	Karagiannis T
2022-11-19	Modified	Wright A

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

Input	UniProt Id
KAT7	O95251

18. Metabolism of carbohydrates (R-HSA-71387)



Starches and sugars are major constituents of the human diet and the catabolism of monosaccharides, notably glucose, derived from them is an essential part of human energy metabolism (Dashty 2013). Glucose can be catabolized to pyruvate (glycolysis) and pyruvate synthesized from diverse sources can be metabolized to form glucose (gluconeogenesis). Glucose can be polymerized to form glycogen under conditions of glucose excess (glycogen synthesis), and glycogen can be broken down to glucose in response to stress or starvation (glycogenolysis). Other monosaccharides prominent in the diet, fructose and galactose, can be converted to glucose. The disaccharide lactose, the major carbohydrate in breast milk, is synthesized in the lactating mammary gland. The pentose phosphate pathway allows the synthesis of diverse monosaccharides from glucose including the pentose ribose-5-phosphate and the regulatory molecule xylulose-5-phosphate, as well as the generation of reducing equivalents for biosynthetic processes. Glycosaminoglycan metabolism and xylulose-5-phosphate synthesis from glucuronate are also annotated as parts of carbohydrate metabolism.

The digestion of dietary starch and sugars and the uptake of the resulting monosaccharides into the circulation from the small intestine are annotated as parts of the “Digestion and absorption” pathway.

References

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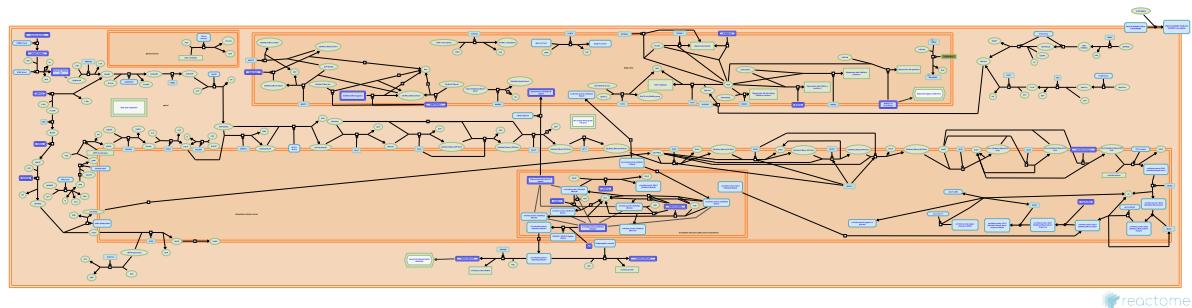
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2003-11-03	Created	Schmidt EE, D'Eustachio P
2010-01-25	Revised	D'Eustachio P
2022-11-17	Edited	Schmidt EE, D'Eustachio P

Date	Action	Author
2022-11-19	Modified	Wright A

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

Input	UniProt Id
B4GALNT2	Q8NHY0

19. Asparagine N-linked glycosylation (R-HSA-446203)



N-linked glycosylation is the most important form of post-translational modification for proteins synthesized and folded in the Endoplasmic Reticulum (Stanley et al. 2009). An early study in 1999 revealed that about 50% of the proteins in the Swiss-Prot database at the time were N-glycosylated (Apweiler et al. 1999). It is now established that the majority of the proteins in the secretory pathway require glycosylation in order to achieve proper folding.

The addition of an N-glycan to a protein can have several roles (Shental-Bechor & Levy 2009). First, glycans enhance the solubility and stability of the proteins in the ER, the Golgi and on the outside of the cell membrane, where the composition of the medium is strongly hydrophilic and where proteins, that are mostly hydrophobic, have difficulty folding properly. Second, N-glycans are used as signal molecules during the folding and transport process of the protein: they have the role of labels to determine when a protein must interact with a chaperon, be transported to the Golgi, or targeted for degradation in case of major folding defects. Third, and most importantly, N-glycans on completely folded proteins are involved in a wide range of processes: they help determine the specificity of membrane receptors in innate immunity or in cell-to-cell interactions, they can change the properties of hormones and secreted proteins, or of the proteins in the vesicular system inside the cell.

All N-linked glycans are derived from a common 14-sugar oligosaccharide synthesized in the ER, which is attached co-translationally to a protein while this is being translated inside the reticulum. The process of the synthesis of this glycan, known as Synthesis of the N-glycan precursor or LLO, constitutes one of the most conserved pathways in eukaryotes, and has been also observed in some eubacteria. The attachment usually happens on an asparagine residue within the consensus sequence asparagine-X-threonine by a complex called oligosaccharyl transferase (OST).

After being attached to an unfolded protein, the glycan is used as a label molecule in the folding process (also known as Calnexin/Calreticulin cycle) (Ledermann 2009). The majority of the glycoproteins in the ER require at least one glycosylated residue in order to achieve proper folding, even if it has been shown that a smaller portion of the proteins in the ER can be folded without this modification.

Once the glycoprotein has achieved proper folding, it is transported via the cis-Golgi through all the Golgi compartments, where the glycan is further modified according to the properties of the glycoprotein. This process involves relatively few enzymes but due to its combinatorial nature, can lead to several millions of different possible modifications. The exact topography of this network of reactions has not been established yet, representing one of the major challenges after the sequencing of the human genome (Hossler et al. 2006).

Since N-glycosylation is involved in a great number of different processes, from cell-cell interaction to folding control, mutations in one of the genes involved in glycan assembly and/or modification can lead to severe development problems (often affecting the central nervous system). All the diseases in genes involved in glycosylation are collectively known as Congenital Disorders of Glycosylation (CDG) (Sparks et al. 2003), and classified as CDG type I for the genes in the LLO synthesis pathway, and CDG type II for the others.

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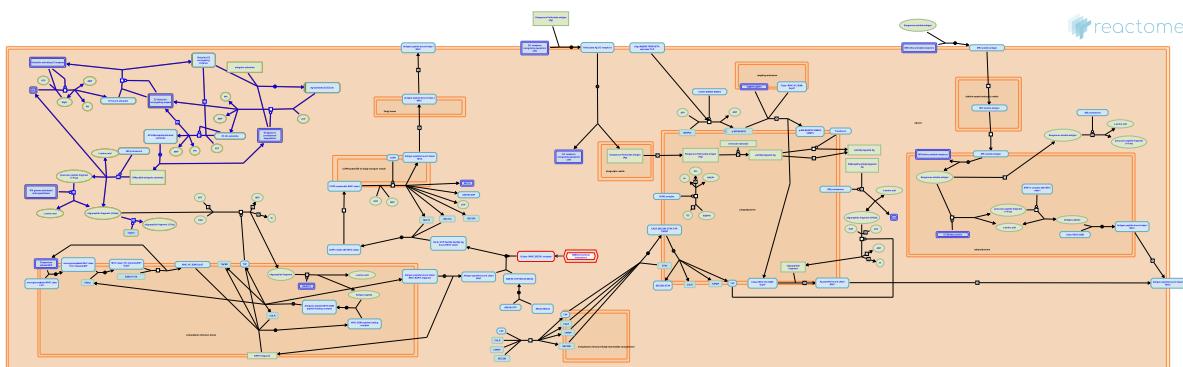
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Date	Action	Author
2009-11-10	Edited	Jassal B
2009-11-10	Authored	Dall'Olio GM
2009-11-10	Created	Jassal B
2010-04-16	Reviewed	Gagneux P
2022-11-19	Modified	Wright A

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

Input	UniProt Id
B4GALNT2	Q8NHY0

20. Antigen processing: Ubiquitination & Proteasome degradation (R-HSA-983168)



Cellular compartments: cytosol.

Intracellular foreign or aberrant host proteins are cleaved into peptide fragments of a precise size, such that they can be loaded on to class I MHC molecules and presented externally to cytotoxic T cells. The ubiquitin-26S proteasome system plays a central role in the generation of these class I MHC antigens.

Ubiquitination is the mechanism of adding ubiquitin to lysine residues on substrate protein leading to the formation of a polyubiquitinated substrate. This process involves three classes of enzyme, an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and an E3 ubiquitin ligase. Polyubiquitination through lysine-48 (K48) generally targets the substrate protein for proteasomal destruction. The protease responsible for the degradation of K48-polyubiquitinated proteins is the 26S proteasome. This proteasome is a two subunit protein complex composed of the 20S (catalytic core) and 19S (regulatory) proteasome complexes. The proteasome eliminates most of the foreign and non-functional proteins from the cell by degrading them into short peptides; only a small fraction of the peptides generated are of the correct length to be presented by the MHC class I system. It has been calculated that between 994 and 3122 protein molecules have to be degraded for the formation of a single, stable MHC class I complex at the cell surface, with an average efficiency of 1 in 2000 (Kloetzel et al. 2004, Princiotta et al. 2003).

References

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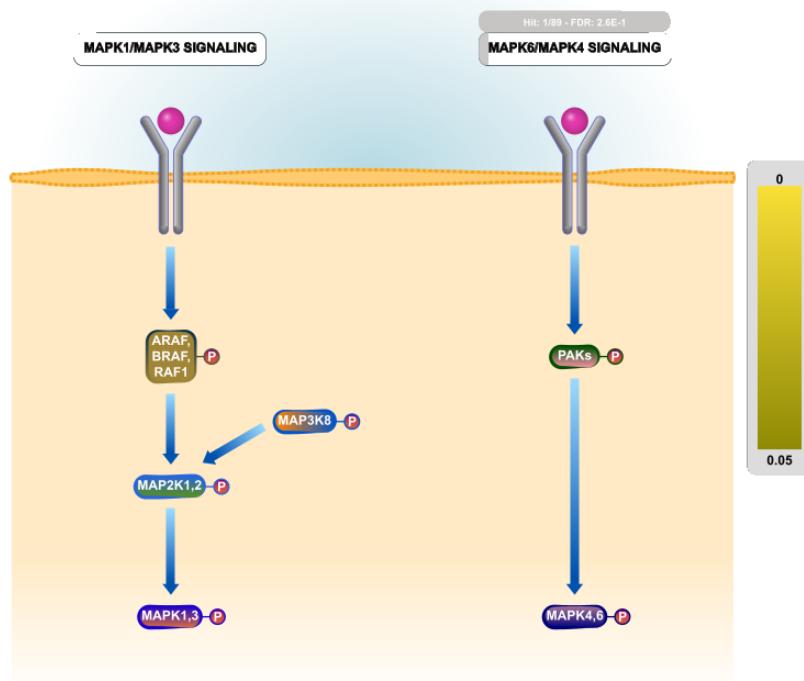
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2010-10-29	Edited	Garapati P V
2010-10-29	Authored	Garapati P V
2010-10-29	Created	Garapati P V
2011-02-11	Reviewed	Elliott T
2022-11-23	Modified	Wright A

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

Input	UniProt Id
UBE2Z	Q9H832

21. MAPK family signaling cascades (R-HSA-5683057)



The mitogen activated protein kinases (MAPKs) are a family of conserved protein serine threonine kinases that respond to varied extracellular stimuli to activate intracellular processes including gene expression, metabolism, proliferation, differentiation and apoptosis, among others.

The classic MAPK cascades, including the ERK1/2 pathway, the p38 MAPK pathway, the JNK pathway and the ERK5 pathway are characterized by three tiers of sequentially acting, activating kinases (reviewed in Kryiakis and Avruch, 2012; Cargnello and Roux, 2011). The MAPK kinase kinase (MAPKKK), at the top of the cascade, is phosphorylated on serine and threonine residues in response to external stimuli; this phosphorylation often occurs in the context of an interaction between the MAPKKK protein and a member of the RAS/RHO family of small GTP-binding proteins. Activated MAPKKK proteins in turn phosphorylate the dual-specificity MAPK kinase proteins (MAPKK), which ultimately phosphorylate the MAPK proteins in a conserved Thr-X-Tyr motif in the activation loop.

Less is known about the activation of the atypical families of MAPKs, which include the ERK3/4 signaling cascade, the ERK7 cascade and the NLK cascade. Although the details are not fully worked out, these MAPK proteins don't appear to be phosphorylated downstream of a 3-tiered kinase system as described above (reviewed in Coulombe and Meloche, 2007; Cargnello and Roux, 2011).

Both conventional and atypical MAPKs are proline-directed serine threonine kinases and, once activated, phosphorylate substrates in the consensus P-X-S/T-P site. Both cytosolic and nuclear targets of MAPK proteins have been identified and upon stimulation, a proportion of the phosphorylated MAPKs relocalize from the cytoplasm to the nucleus. In some cases, nuclear translocation may be accompanied by dimerization, although the relationship between these two events is not fully elaborated (reviewed in Kryiakis and Avruch, 2012; Cargnello and Roux, 2011; Plotnikov et al, 2010).

References

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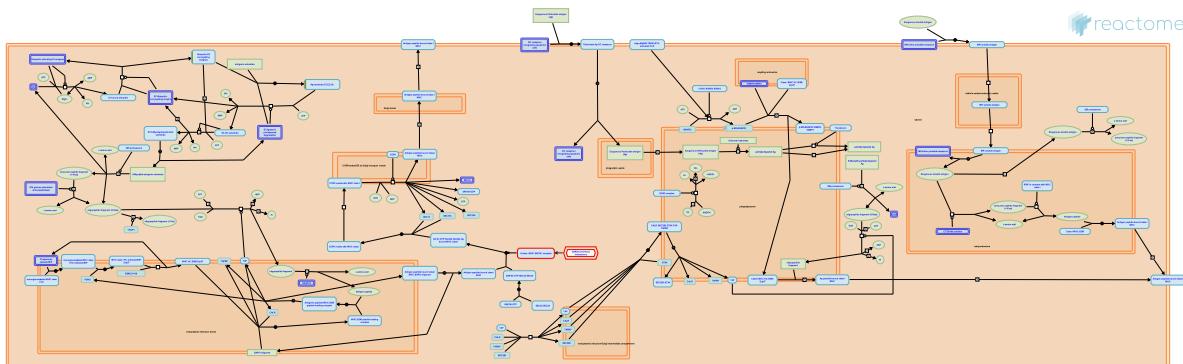
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2015-03-10	Authored	Rothfels K
2015-03-11	Created	Rothfels K
2015-04-29	Reviewed	Roskoski R Jr
2022-11-19	Modified	Wright A

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

Input	UniProt Id
IGF2BP1	Q9NZI8

22. Class I MHC mediated antigen processing & presentation ([R-HSA-983169](#))



Major histocompatibility complex (MHC) class I molecules play an important role in cell mediated immunity by reporting on intracellular events such as viral infection, the presence of intracellular bacteria or tumor-associated antigens. They bind peptide fragments of these proteins and presenting them to CD8+ T cells at the cell surface. This enables cytotoxic T cells to identify and eliminate cells that are synthesizing abnormal or foreign proteins. MHC class I is a trimeric complex composed of a polymorphic heavy chain (HC or alpha chain) and an invariable light chain, known as beta2-microglobulin (B2M) plus an 8-10 residue peptide ligand. Represented here are the events in the biosynthesis of MHC class I molecules, including generation of antigenic peptides by the ubiquitin/26S-proteasome system, delivery of these peptides to the endoplasmic reticulum (ER), loading of peptides to MHC class I molecules and display of MHC class I complexes on the cell surface.

References

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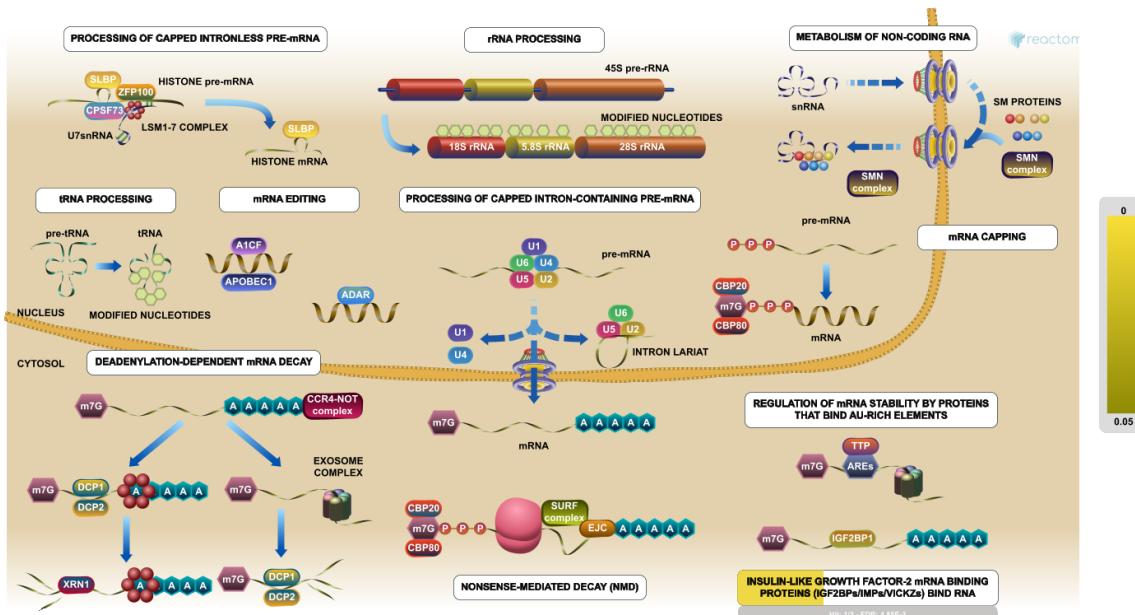
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Date	Action	Author
2010-10-29	Edited	Garapati P V
2010-10-29	Authored	Garapati P V
2010-10-29	Created	Garapati P V
2011-02-11	Reviewed	Elliott T
2022-11-19	Modified	Wright A

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

Input	UniProt Id
UBE2Z	Q9H832

23. 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 polyadenylation 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

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

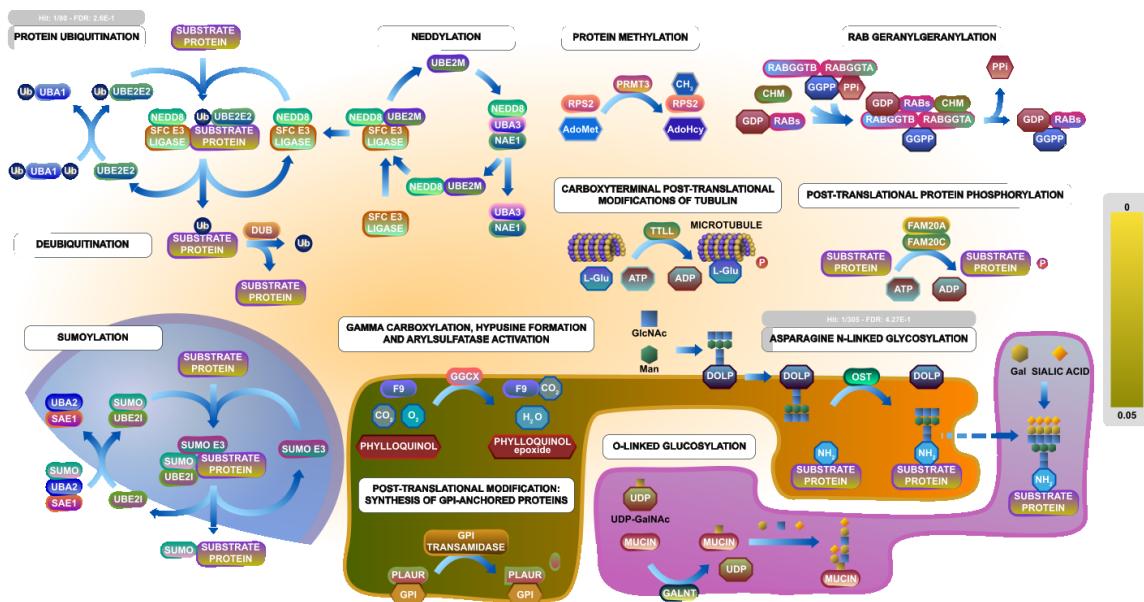
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2016-12-29	Edited	D'Eustachio P
2016-12-29	Authored	D'Eustachio P
2016-12-29	Created	D'Eustachio P
2016-12-30	Revised	D'Eustachio P
2017-02-28	Reviewed	Gillespie ME
2022-11-19	Modified	Wright A

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

Input	UniProt Id
IGF2BP1	Q9NZI8

24. Post-translational protein modification (R-HSA-597592)



After translation, many newly formed proteins undergo further covalent modifications that alter their functional properties. Modifications associated with protein localization include the attachment of oligosaccharide moieties to membrane-bound and secreted proteins (**N-linked** and **O-linked glycosylation**), the attachment of lipid (**RAB geranylgeranylation**) or glycolipid moieties (**GPI-anchored proteins**) that anchor proteins to cellular membranes, and the vitamin K-dependent attachment of carboxyl groups to glutamate residues. Modifications associated with functions of specific proteins include **gamma carboxylation** of clotting factors, **hypusine formation** on eukaryotic translation initiation factor 5A, conversion of a cysteine residue to formylglycine (**aryl-sulfatase activation**), methylation of lysine and arginine residues on non-histone proteins (**protein methylation**), **protein phosphorylation** by secretory pathway kinases, and **carboxyterminal modifications of tubulin** involving the addition of polyglutamate chains.

Protein ubiquitination and **deubiquitination** play a major role in regulating protein stability and, together with **SUMOylation** and **neddylation**, can modulate protein function as well.

References

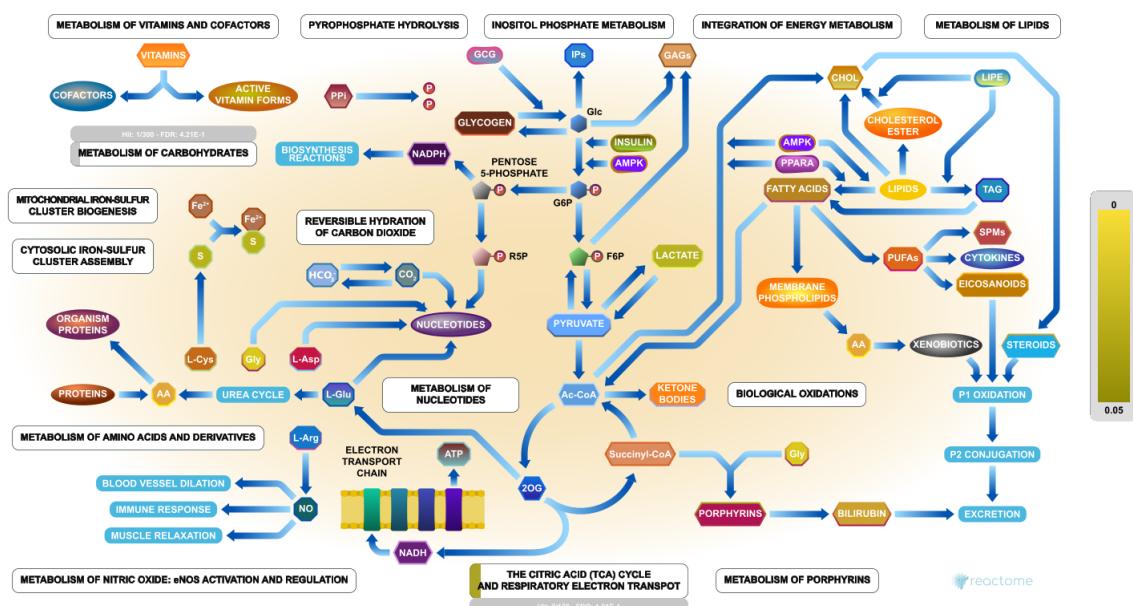
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2010-04-14	Created	D'Eustachio P
2022-11-17	Edited	D'Eustachio P
2022-11-17	Reviewed	Stafford DW, Orlean P
2022-11-19	Modified	Wright A

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

Input	UniProt Id	Input	UniProt Id
B4GALNT2	Q8NHY0	UBE2Z	Q9H832

25. Metabolism (R-HSA-1430728)



Metabolic processes in human cells generate energy through the oxidation of molecules consumed in the diet and mediate the synthesis of diverse essential molecules not taken in the diet as well as the inactivation and elimination of toxic ones generated endogenously or present in the extracellular environment. The processes of energy metabolism can be classified into two groups according to whether they involve carbohydrate-derived or lipid-derived molecules, and within each group it is useful to distinguish processes that mediate the breakdown and oxidation of these molecules to yield energy from ones that mediate their synthesis and storage as internal energy reserves. Synthetic reactions are conveniently grouped by the chemical nature of the end products, such as nucleotides, amino acids and related molecules, and porphyrins. Detoxification reactions (biological oxidations) are likewise conveniently classified by the chemical nature of the toxin.

At the same time, all of these processes are tightly integrated. Intermediates in reactions of energy generation are starting materials for biosyntheses of amino acids and other compounds, broad-specificity oxidoreductase enzymes can be involved in both detoxification reactions and biosyntheses, and hormone-mediated signaling processes function to coordinate the operation of energy-generating and energy-storing reactions and to couple these to other biosynthetic processes.

References

Edit history

Date	Action	Author
2011-07-07	Created	Jassal B
2022-11-19	Modified	Wright A

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

Input	UniProt Id	Input	UniProt Id
ATP5MC1	P05496, Q06055	B4GALNT2	Q8NHY0

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.

5 of the submitted entities were found, mapping to 6 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATP5MC1	P05496, Q06055	B4GALNT2	Q8NHY0	IGF2BP1	Q9NZI8
KAT7	O95251	UBE2Z	Q9H832		

7. Identifiers not found

These 15 identifiers were not found neither mapped to any entity in Reactome.

CALCOCO2	ENSG00000204584	ENSG00000250838	ENSG00000251461	ENSG00000262837	FAM117A	HOXB13	HOXB5
LOC124904020	LOC124904116	NFE2L1-DT		NXPH3	PRAC1	PRAC2	TAC4