reactome

Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 77 on 24/08/2021. The web link to these results is:

https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMTA4MjQxODI0MjBfNTY5

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:

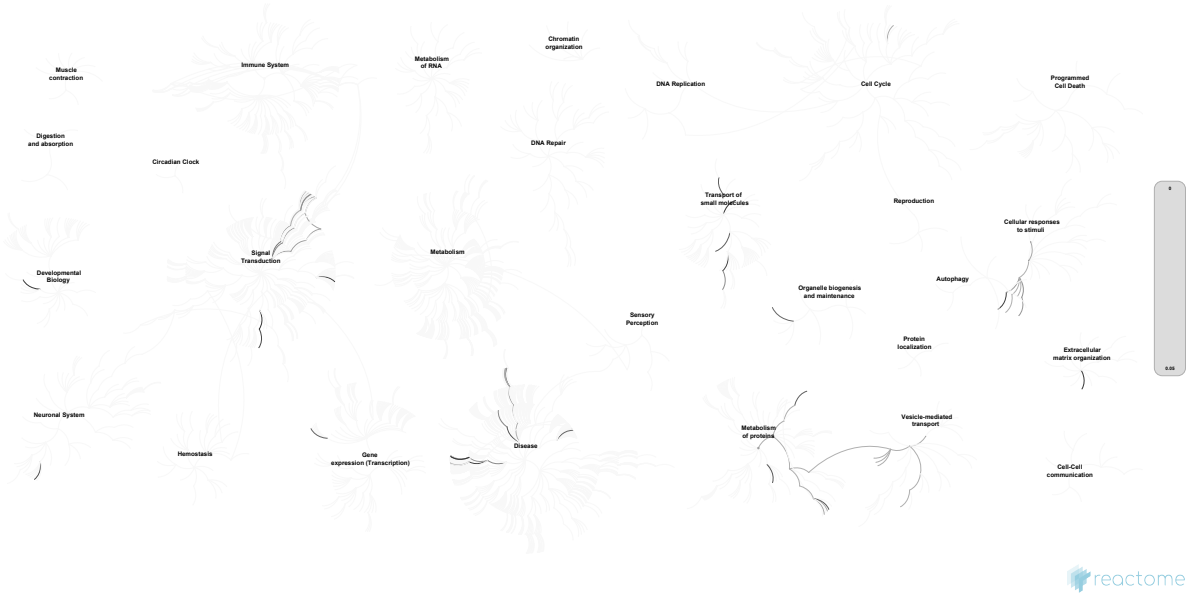
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, … D'Eustachio P (2016). The reactome pathway knowledgebase. Nucleic Acids Research, 44(D1), D481–D487. https://doi.org/10.1093/nar/gkv1351.

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.
- 73 out of 118 identifiers in the sample were found in Reactome, where 261 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 MjAyMTA4MjQxODI0MjBfNTY5. 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.

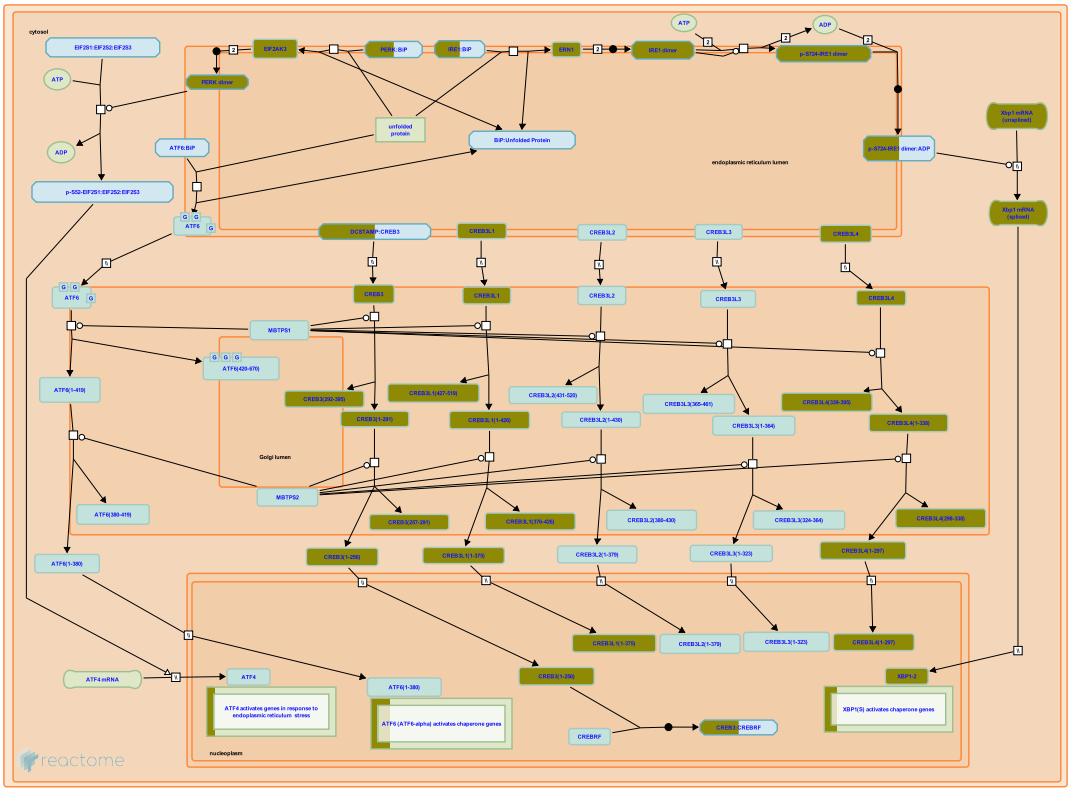
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Unfolded Protein Response (UPR)	19 / 155	0.011	2.33e-15	6.23e-13	70 / 94	0.007
Asparagine N-linked glycosylation	27 / 421	0.029	1.38e-14	1.83e-12	39 / 144	0.011
ER to Golgi Anterograde Transport	16 / 164	0.011	1.21e-11	7.96e-10	27 / 39	0.003
Transport to the Golgi and subsequent modification	17 / 219	0.015	8.90e-11	4.72e-09	29 / 60	0.004
IRE1alpha activates chaperones	12 / 101	0.007	5.60e-10	2.46e-08	52 / 53	0.004
COPI-mediated anterograde transport	11 / 107	0.007	1.30e-08	4.31e-07	10 / 12	8.88e-04
XBP1(S) activates chaperone genes	9 / 95	0.007	5.58e-07	1.62e-05	47 / 47	0.003
Signaling by FGFR2 IIIa TM	5 / 24	0.002	4.87e-06	1.16e-04	2 / 2	1.48e-04
Post-translational protein modification	35 / 1,598	0.11	4.92e-06	1.16e-04	60 / 526	0.039
FGFR2 mutant receptor activation	6 / 43	0.003	5.25e-06	1.16e-04	17 / 18	0.001
Synthesis of substrates in N-glycan biosythesis	9 / 131	0.009	7.45e-06	1.49e-04	9 / 49	0.004
Signaling by FGFR2 in disease	6 / 58	0.004	2.80e-05	5.33e-04	27 / 28	0.002
Biosynthesis of the N-glycan precursor (dolichol lipid-linked oligosaccharide, LLO) and transfer to a nascent protein	9 / 159	0.011	3.37e-05	5.52e-04	9 / 63	0.005
Membrane Trafficking	19 / 665	0.046	3.45e-05	5.52e-04	47 / 219	0.016
O-linked glycosylation of mucins	6 / 73	0.005	9.87e-05	0.001	17 / 17	0.001
COPI-dependent Golgi-to-ER retrograde traffic	7 / 107	0.007	1.07e-04	0.001	6 / 11	8.14e-04
CREB3 factors activate genes	3 / 9	6.19e-04	1.08e-04	0.002	13 / 21	0.002
Phospholipase C-mediated cascade; FGFR2	4 / 25	0.002	1.24e-04	0.002	3 / 3	2.22e-04
COPII-mediated vesicle transport	6 / 77	0.005	1.32e-04	0.002	11 / 16	0.001
FGFR2 ligand binding and activation	4 / 26	0.002	1.44e-04	0.002	4 / 5	3.70e-04
Signaling by FGFR in disease	6 / 82	0.006	1.84e-04	0.002	27 / 106	0.008
Synthesis of GDP-mannose	3 / 11	7.56e-04	1.95e-04	0.002	2 / 3	2.22e-04
PI-3K cascade:FGFR2	4 / 31	0.002	2.80e-04	0.003	6 / 7	5.18e-04
Metabolism of proteins	38 / 2,205	0.152	3.50e-04	0.003	65 / 798	0.059
SHC-mediated cascade:FGFR2	4 / 33	0.002	3.54e-04	0.003	4 / 4	2.96e-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. Unfolded Protein Response (UPR) (R-HSA-381119)



Cellular compartments: Golgi membrane, cytosol, endoplasmic reticulum lumen, endoplasmic reticulum membrane, nucleoplasm.

The Unfolded Protein Response (UPR) is a regulatory system that protects the Endoplasmic Reticulum (ER) from overload. The UPR is provoked by the accumulation of improperly folded protein in the ER during times of unusually high secretion activity. Analysis of mutants with altered UPR, however, shows that the UPR is also required for normal development and function of secretory cells.

One level at which the URP operates is transcriptional and translational regulation: mobilization of ATF6, ATF6B, CREB3 factors and IRE1 leads to increased transcription of genes encoding chaperones, while mobilization of PERK (pancreatic eIF2alpha kinase, EIF2AK3) leads to phosphorylation of the translation initiation factor eIF2alpha and global down-regulation of protein synthesis.

ATF6, ATF6B, and CREB3 factors (CREB3 (LUMAN), CREB3L1 (OASIS), CREB3L2 (BBF2H7, Tisp40), CREB3L3 (CREB-H), and CREB3L4 (CREB4)) are membrane-bound transcription activators that respond to ER stress by transiting from the ER membrane to the Golgi membrane where their transmembrane domains are cleaved, releasing their cytosolic domains to transit to the nucleus and activate transcription of target genes. IRE1, also a resident of the ER membrane, dimerizes and autophosphorylates in response to ER stress. The activated IRE1 then catalyzes unconventional splicing of XBP1 mRNA to yield an XBP1 isoform that is targeted to the nucleus and activates chaperone genes.

References

Schröder M (2008). Endoplasmic reticulum stress responses. Cell Mol Life Sci, 65, 862-94.

Credle JJ, Finer-Moore JS, Papa FR, Stroud RM & Walter P (2005). On the mechanism of sensing unfolded protein in the endoplasmic reticulum. Proc Natl Acad Sci U S A, 102, 18773-84.

Schröder M & Kaufman RJ (2005). The mammalian unfolded protein response. Annu Rev Biochem, 74, 739-89.

Eizirik DL, Cardozo AK & Cnop M (2008). The role for endoplasmic reticulum stress in diabetes mellitus. Endocr Rev, 29, 42-61.

Scheuner D & Kaufman RJ (2008). The unfolded protein response: a pathway that links insulin demand with beta-cell failure and diabetes. Endocr Rev, 29, 317-33.

Edit history

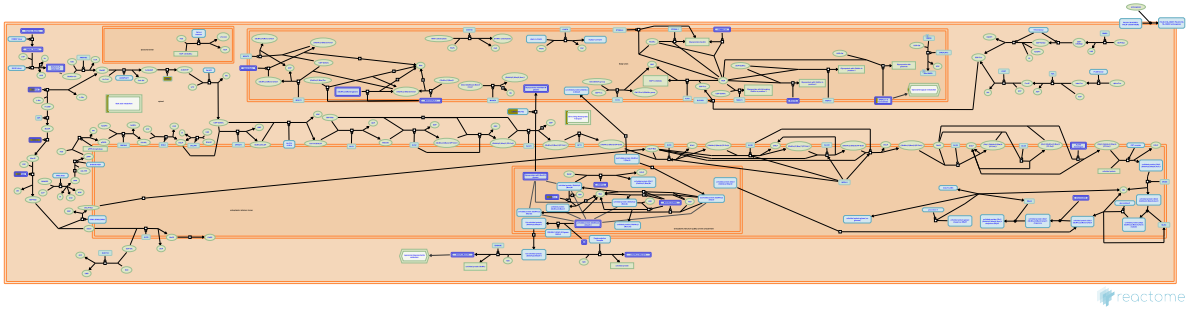
Date	Action	Author
2008-11-19	Created	May B
2008-11-20	Edited	May B, Gopinathrao G
2008-12-02	Reviewed	Matthews L, D'Eustachio P, Gillespie ME
2009-06-02	Authored	May B
2010-04-30	Reviewed	Urano F
2021-05-22	Modified	Shorser S

Entities found in this pathway (10)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3	CREB3L1	Q96BA8	CREB3L4	O43889, Q8TEY5
EIF2AK3	Q9NZJ5	ERN2	O75460	GFPT1	Q06210
HERPUD1	Q15011	KDELR3	O43731	PDIA5	Q14554
XBP1	P17861-2				

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
ARFGAP1	ENSG00000101199	GFPT1	ENSG00000198380	HERPUD1	ENSG00000051108
KDELR3	ENSG00000100196	PDIA5	ENSG00000065485	XBP1	ENSG00000100219, ENST00000216037, ENST00000344347

2. 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 an 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) (Lederkremer 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 an 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.

References

Stanley P, Stanley P, Schachter H, Taniguchi N, Varki A, Cummings RD, ... Etzler ME (2009). *N-Glycans* .

Sparks SE, Krasnewich DM, Pagon RA, Bird TC, Dolan CR & Stephens K (1993). *Congenital Disorders of Glycosylation Overview* .

Apweiler R, Hermjakob H & Sharon N (1999). On the frequency of protein glycosylation, as deduced from analysis of the SWISS-PROT database. Biochim Biophys Acta, 1473, 4-8.

Shental-Bechor D & Levy Y (2009). Folding of glycoproteins: toward understanding the biophysics of the glycosylation code. Curr Opin Struct Biol, 19, 524-33.

Lederkremer GZ (2009). Glycoprotein folding, quality control and ER-associated degradation. Curr Opin Struct Biol, 19, 515-23.

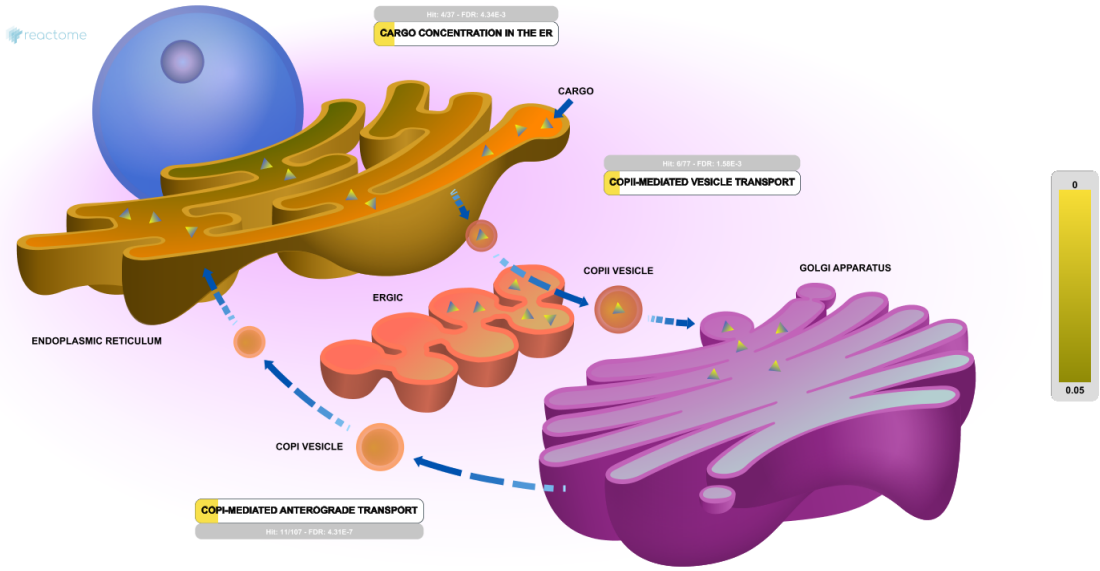
Edit history

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
2021-05-22	Modified	Shorser S

Entities found in this pathway (23)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3, Q9NP61	B4GALT4	O60513	COG3	Q96JB2
COPB2	P35606	EDEM3	Q9BZQ6	GFPT1	Q06210
GMPPB	Q9Y5P6	GNE	Q9Y223	GOLGA2	Q08379
GOLGB1	Q14789	KDELR2	P24390, P33947	KDELR3	O43731
LMAN1	P49257, Q9HAT1	MIA3	Q5JRA6	NANS	Q9NR45
PGM3	O95394	PMM2	O15305, Q92871	SEC16A	O15027
SEC24D	O94855	SLC35A1	P78382	ST6GALNAC1	Q9NSC7
TMED3	Q9Y3Q3	USO1	O60763		

3. ER to Golgi Anterograde Transport (R-HSA-199977)



Secretory cargo destined to be secreted or to arrive at the plasma membrane (PM) leaves the ER via distinct exit sites. This cargo is destined for the Golgi apparatus for further processing.

About 25% of the proteome may be exported from the ER in human cells. This cargo is recognized and concentrated into COPII vesicles, which range in size from 60-90 nm, and move cargo from the ER to the ERGIC. Soluble cargo in the ER lumen is concentrated into COPII vesicles through interaction with a receptor with the receptor subsequently recycled to the ER in COPI vesicles through retrograde traffic.

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.

Retrograde traffic makes use of microtubule-directed COPI-coated vesicles, carrying ER proteins and membrane back to the ER.

References

Kirchhausen Tomas (2000). Three ways to make a vesicle. Nat Rev Mol Cell Biol, 1, 187-98.

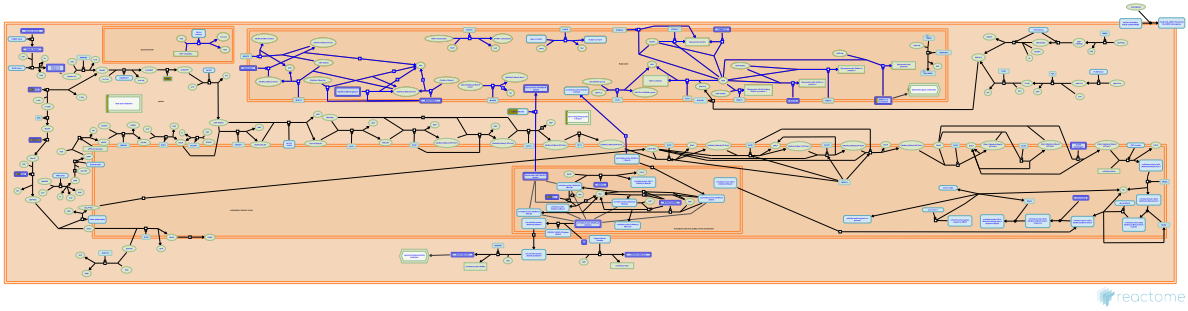
Edit history

Date	Action	Author
2007-07-14	Authored	Gillespie ME
2007-07-14	Created	Gillespie ME
2007-07-19	Edited	Gillespie ME
2010-11-18	Reviewed	Gagneux P
2015-04-18	Revised	Rothfels K
2015-08-18	Revised	Gillespie ME
2021-05-22	Modified	Shorser S

Entities found in this pathway (13)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3, Q9NP61	COG3	Q96JB2	COPB2	P35606
GOLGA2	Q08379	GOLGB1	Q14789	KDELR2	P24390, P33947
KDELR3	O43731	LMAN1	P49257, Q9HAT1	MIA3	Q5JRA6
SEC16A	O15027	SEC24D	O94855	TMED3	Q9Y3Q3
USO1	O60763				

4. Transport to the Golgi and subsequent modification (R-HSA-948021)



At least two mechanisms of transport of proteins from the ER to the Golgi have been described. One is a general flow requiring no export signals (Wieland et al, 1987; Martinez-Menarguez et al, 1999). The other is mediated by LMAN1/MCFD2, mannose-binding lectins that recognize a glycan signal (Zhang B et al, 2003).

References

Zhang B, Cunningham MA, Nichols WC, Bernat JA, Seligsohn U, Pipe SW, ... Ginsburg D (2003). Bleeding due to disruption of a cargo-specific ER-to-Golgi transport complex. Nat Genet, 34, 220-5.

Wieland FT, Gleason ML, Serafini TA & Rothman JE (1987). The rate of bulk flow from the endoplasmic reticulum to the cell surface. Cell, 50, 289-300.

Martinez-Menárguez JA, Geuze HJ, Slot JW & Klumperman J (1999). Vesicular tubular clusters between the ER and Golgi mediate concentration of soluble secretory proteins by exclusion from COPI-coated vesicles. Cell, 98, 81-90.

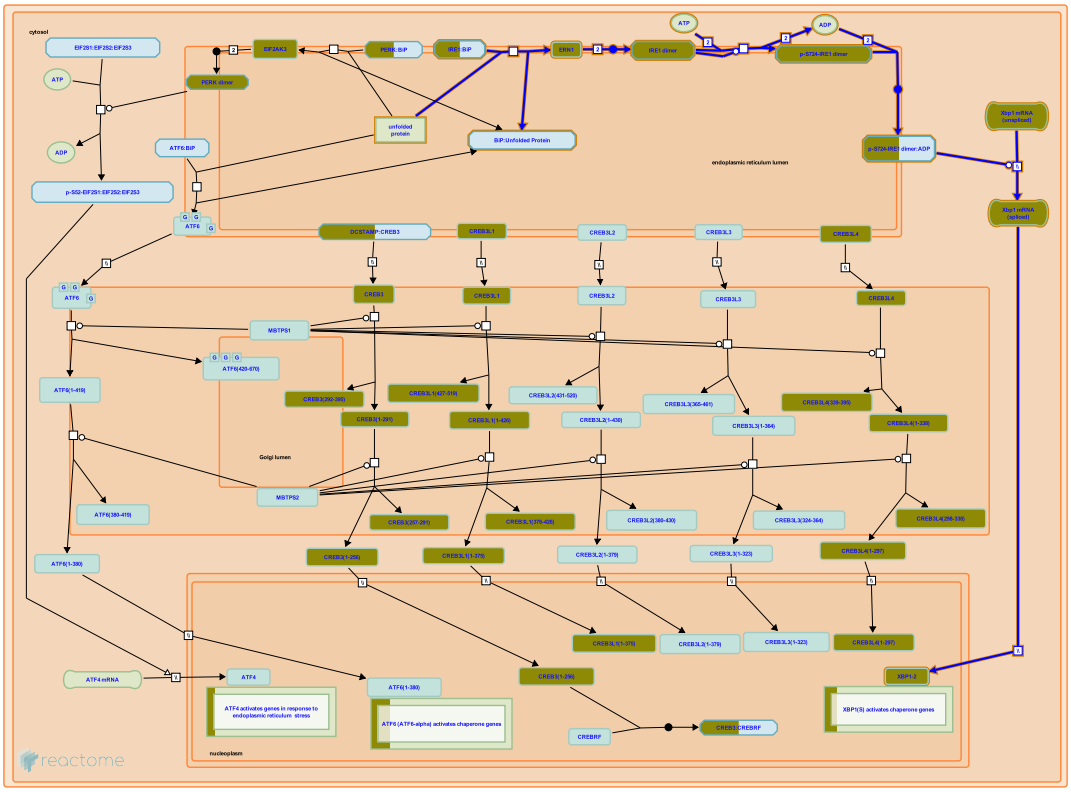
Edit history

Date	Action	Author
2009-11-10	Authored	Dall'Olio GM
2010-09-15	Edited	Jassal B
2010-09-15	Created	Jassal B
2010-11-18	Reviewed	Gagneux P
2021-05-22	Modified	Shorser S

Entities found in this pathway (14)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3, Q9NP61	B4GALT4	O60513	COG3	Q96JB2
COPB2	P35606	GOLGA2	Q08379	GOLGB1	Q14789
KDELR2	P24390, P33947	KDELR3	O43731	LMAN1	P49257, Q9HAT1
MIA3	Q5JRA6	SEC16A	O15027	SEC24D	O94855
TMED3	Q9Y3Q3	USO1	O60763		

5. IRE1alpha activates chaperones (R-HSA-381070)



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

IRE1-alpha is a single-pass transmembrane protein that resides in the endoplasmic reticulum (ER) membrane. The C-terminus of IRE1-alpha is located in the cytosol; the N-terminus is located in the ER lumen. In unstressed cells IRE1-alpha exists in an inactive heterodimeric complex with BiP such that BiP in the ER lumen binds the N-terminal region of IRE1-alpha. Upon accumulation of unfolded proteins in the ER, BiP binds the unfolded protein and the IRE1-alpha:BiP complex dissociates. The dissociated IRE1-alpha then forms homodimers. Initially the luminal N-terminal regions pair. This is followed by trans-autophosphorylation of IRE1-alpha at Ser724 in the cytosolic C-terminal region. The phosphorylation causes a conformational change that allows the dimer to bind ADP, causing a further conformational change to yield back-to-back pairing of the cytosolic C-terminal regions of IRE1-alpha. The fully paired IRE1-alpha homodimer has endoribonuclease activity and cleaves the mRNA encoding Xbp-1. A 26 residue polyribonucleotide is released and the 5' and 3' fragments of the original Xbp-1 mRNA are rejoined. The spliced Xbp-1 message encodes Xbp-1 (S), a potent activator of transcription. Xbp-1 (S) together with the ubiquitous transcription factor NF-Y bind the ER Stress Responsive Element (ERSE) in a number of genes encoding chaperones. Recent data suggest that the IRE1-alpha homodimer can also cleave specific subsets of mRNAs, including the insulin (INS) mRNA in pancreatic beta cells.

References

Eizirik DL, Cardozo AK & Cnop M (2008). The role for endoplasmic reticulum stress in diabetes mellitus. Endocr Rev, 29, 42-61.

Scheuner D & Kaufman RJ (2008). The unfolded protein response: a pathway that links insulin demand with beta-cell failure and diabetes. Endocr Rev, 29, 317-33.

Schröder M (2008). Endoplasmic reticulum stress responses. Cell Mol Life Sci, 65, 862-94.

Edit history

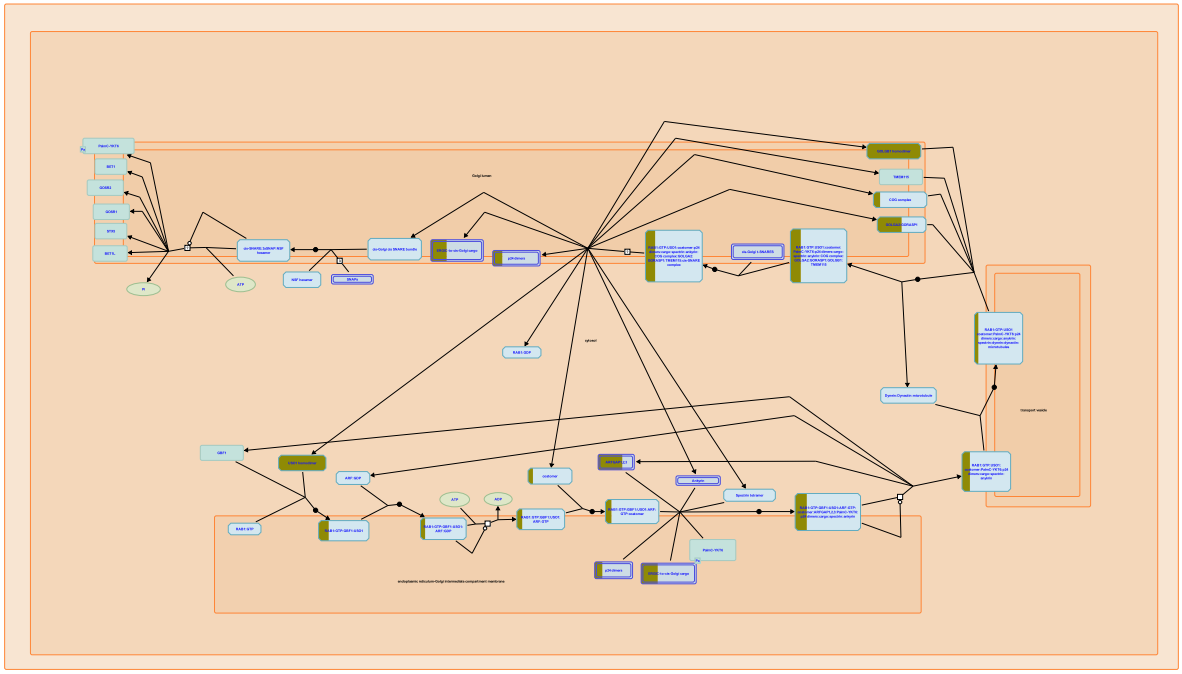
Date	Action	Author
2008-11-19	Created	May B
2008-11-20	Edited	May B, Gopinathrao G
2008-12-02	Reviewed	Matthews L, D'Eustachio P, Gillespie ME
2009-06-02	Authored	May B
2010-04-30	Reviewed	Urano F
2021-05-22	Modified	Shorser S

Entities found in this pathway (6)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3	ERN2	O75460	GFPT1	Q06210
KDELR3	O43731	PDIA5	Q14554	XBP1	P17861-2

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
ARFGAP1	ENSG00000101199	GFPT1	ENSG00000198380	KDELR3	ENSG00000100196
PDIA5	ENSG00000065485	XBP1	ENST00000216037, ENST00000344347		

6. 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
2021-05-22	Modified	Shorser S

Entities found in this pathway (9)

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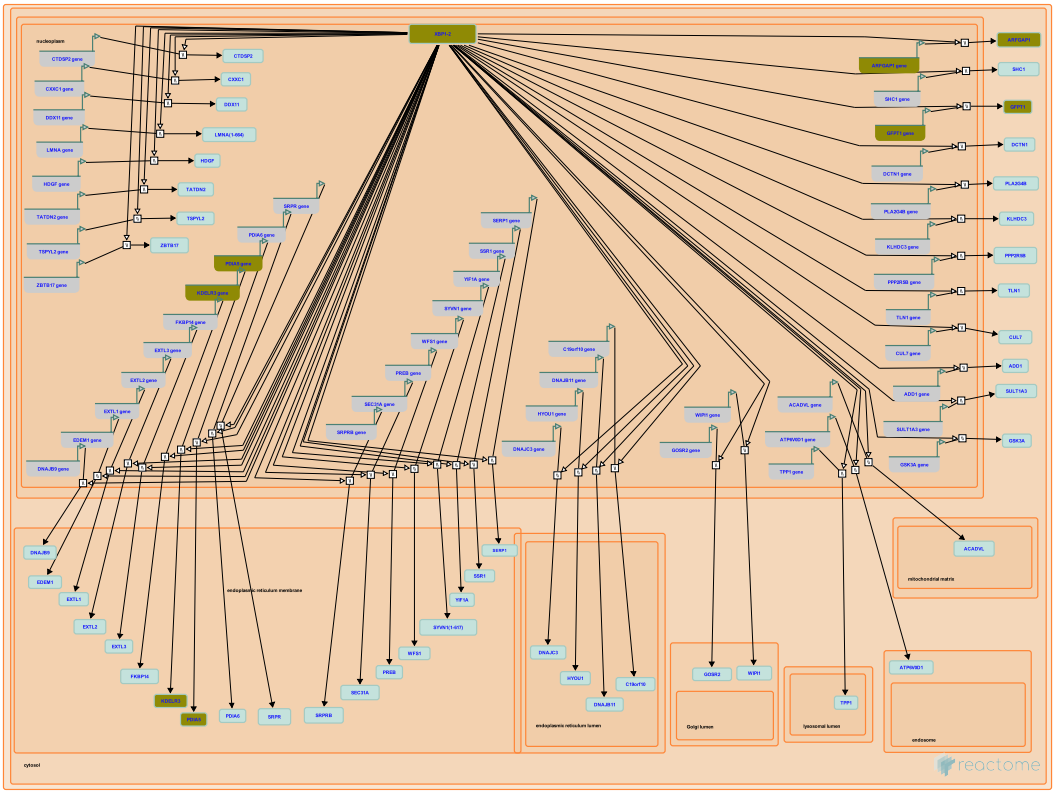
ARFGAP1	Q8N6T3, Q9NP61	COG3	Q96JB2	COPB2	P35606
GOLGA2	Q08379	GOLGB1	Q14789	KDELR2	P24390, P33947
KDELR3	O43731	TMED3	Q9Y3Q3	USO1	O60763

7. XBP1(S) activates chaperone genes (R-HSA-381038)



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

Xbp-1 (S) binds the sequence CCACG in ER Stress Responsive Elements (ERSE, consensus sequence CCAAT (N)9 CCACG) located upstream from many genes. The ubiquitous transcription factor NF-Y, a heterotrimer, binds the CCAAT portion of the ERSE and together the IRE1-alpha: NF-Y complex activates transcription of a set of chaperone genes including DNAJB9, EDEM, RAMP4, p58IPK, and others. This results in an increase in protein folding activity in the ER.

References

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Yoshida H, Oku M, Suzuki M & Mori K (2006). pXBP1(U) encoded in XBP1 pre-mRNA negatively regulates unfolded protein response activator pXBP1(S) in mammalian ER stress response. J Cell Biol, 172, 565-75.

Lee AH, Iwakoshi NN & Glimcher LH (2003). XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. Mol Cell Biol, 23, 7448-59.

Acosta-Alvear D, Zhou Y, Blais A, Tsikitis M, Lents NH, Arias C, ... Dynlacht BD (2007). XBP1 controls diverse cell type- and condition-specific transcriptional regulatory networks. Mol Cell, 27, 53-66.

Yamamoto K, Suzuki N, Wada T, Okada T, Yoshida H, Kaufman RJ & Mori K (2008). Human HRD1 promoter carries a functional unfolded protein response element to which XBP1 but not ATF6 directly binds. J Biochem, 144, 477-86.

Edit history

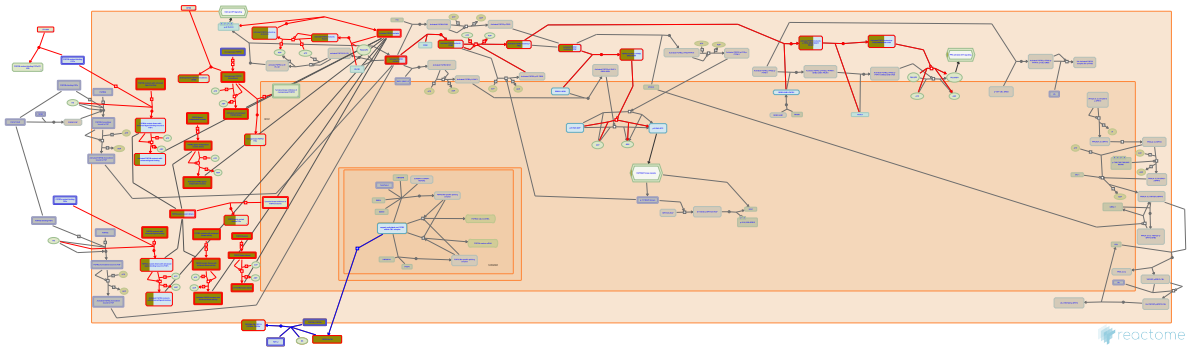
Date	Action	Author
2008-11-19	Created	May B
2008-12-02	Reviewed	Matthews L, D'Eustachio P, Gillespie ME
2009-06-02	Edited	May B
2009-06-02	Authored	May B
2010-04-30	Reviewed	Urano F
2018-11-25	Modified	May B

Entities found in this pathway (5)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3	GFPT1	Q06210	KDELR3	O43731
PDIA5	Q14554	XBP1	P17861-2		

Input	Ensembl Id	Input	Ensembl Id
ARFGAP1	ENSG00000101199	GFPT1	ENSG00000198380
KDELR3	ENSG00000100196	PDIA5	ENSG00000065485

8. Signaling by FGFR2 IIIa TM (R-HSA-8851708)



Diseases: acrocephalosyndactylia.

A soluble truncated form of FGFR2 is aberrantly expressed in an Apert Syndrome mouse model and inhibits FGFR signaling in vitro and in vivo. This variant, termed FGFR IIIa TM, arises from an mis-spliced transcript that fuses exon 7 to exon 10 and that escapes nonsense-mediated decay. FGFR2 IIIa TM may inhibit signaling by sequestering FGF ligand and/or by forming nonfunctional heterodimers with full-length receptors at the cell surface (Wheldon et al, 2011).

References

Wheldon LM, Khodabukus N, Patey SJ, Smith TG, Heath JK & Hajihosseini MK (2011). Identification and characterization of an inhibitory fibroblast growth factor receptor 2 (FGFR2) molecule, up-regulated in an Apert Syndrome mouse model. Biochem. J., 436, 71-81.

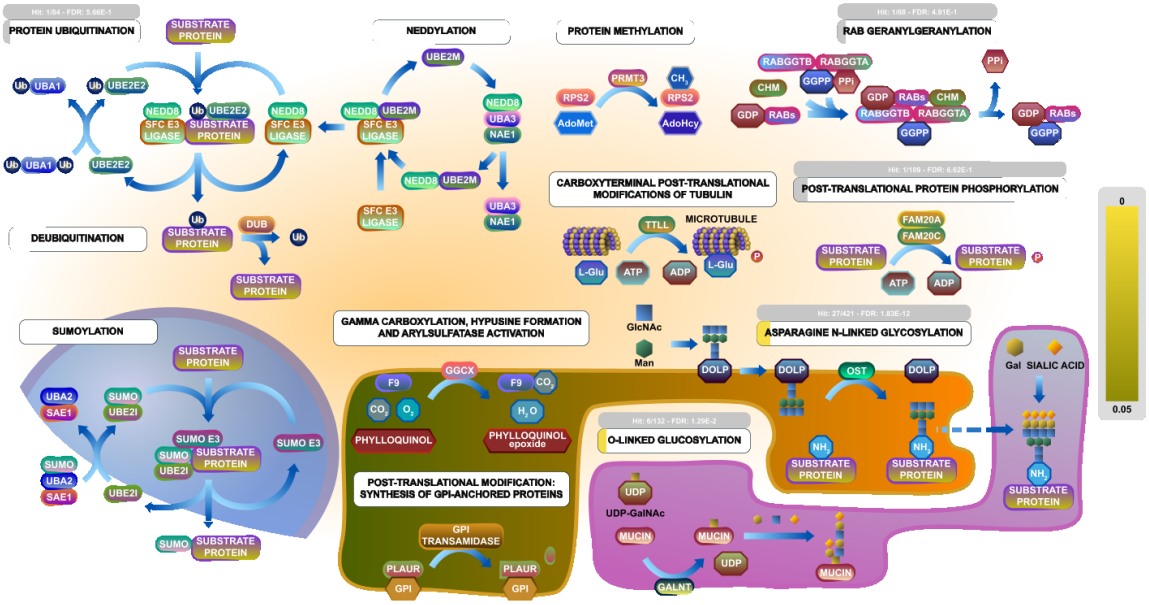
Edit history

Date	Action	Author
2016-01-09	Edited	Rothfels K
2016-01-09	Authored	Rothfels K
2016-01-09	Created	Rothfels K
2016-01-25	Modified	Rothfels K
2016-01-25	Reviewed	Grose RP

Entities found in this pathway (1)

Input	UniProt Id
FGFR2	P21802, P21802-1, P21802-18, P21802-3, P21802-5

9. 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 (**arylsulfatase 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

Edit history

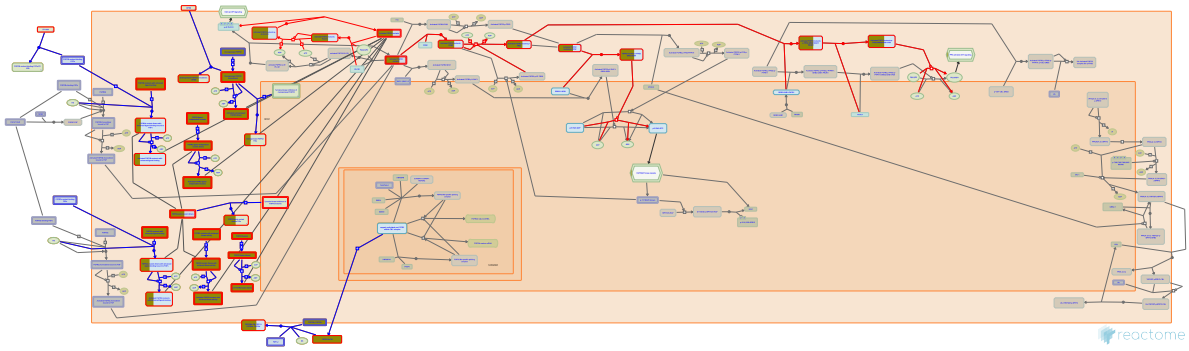
Date	Action	Author
2005-04-18	Authored	D'Eustachio P
2010-04-14	Created	D'Eustachio P
2021-05-18	Edited	D'Eustachio P
2021-05-18	Reviewed	Stafford DW, Orlean P
2021-05-22	Modified	Shorser S

Entities found in this pathway (31)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3, Q9NP61	ATOH1	P61086	B4GALT4	O60513

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
COG3	Q96JB2	COPB2	P35606	EDEM3	Q9BZQ6
GALNT12	Q8IXK2	GALNT5	Q7Z7M9	GALNT7	Q86SF2
GALNT8	Q9NY28	GFPT1	Q06210	GMPPB	Q9Y5P6
GNE	Q9Y223	GOLGA2	Q08379	GOLGB1	Q14789
KDELR2	P24390, P33947	KDELR3	O43731	LMAN1	P49257, Q9HAT1
MIA3	Q5JRA6	MUC2	Q02817	MUC4	Q99102
NANS	Q9NR45	PGM3	O95394	PMM2	O15305, Q92871
RAB27A	P51159	SEC16A	O15027	SEC24D	O94855
SLC35A1	P78382	ST6GALNAC1	Q9NSC7	TMED3	Q9Y3Q3
USO1	O60763				

10. FGFR2 mutant receptor activation (R-HSA-1839126)



Cellular compartments: plasma membrane, cytosol, extracellular region.

Diseases: cancer, bone development disease.

Autosomal dominant mutations in FGFR2 are associated with the development of a range of skeletal disorders including Beare-Stevensen cutis gyrata syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome, Crouzon syndrome and Apert Syndrome (reveiwed in Burke, 1998; Webster and Donoghue 1997; Cunningham, 2007). Activating point mutations have also been identified in FGFR2 in ~15% of endometrial cancers, as well as to a lesser extent in ovarian and gastric cancers (Dutt, 2008; Pollock, 2007; Byron, 2010; Jang, 2001). Activating mutations in FGFR2 are thought to contribute to receptor activation through diverse mechanisms, including constitutive ligand-independent dimerization (Robertson, 1998), expanded range and affinity for ligand (Ibrahimi, 2004b; Yu, 2000) and enhanced kinase activity (Byron, 2008; Chen, 2007). FGFR2 amplifications have been identified in 10% of gastric cancers, where they are associated with poor prognosis diffuse cancers (Hattori, 1996; Ueda, 1999; Shin, 2000; Kunii, 2008) , and in ~1% of breast cancers (Turner, 2010; Tannheimer, 2000). FGFR2 amplification often occur in conjunction with deletions of C-terminal exons, resulting in expression of a internalization- and degradation-resistant form of the receptor (Takeda, 2007; Cha, 2008, 2009). Signaling through overexpressed FGFR2 shows evidence of being ligand-independent and sensitive to FGFR inhibitors (Lorenzi, 1997; Takeda, 2007; Cha, 2009). More recently, FGFR2 fusion proteins have been identified in a number of cancers; these are thought to form constitutive ligand-independent dimers based on the dimerization domains of the 3' fusion partners and contribute to cellular proliferation and tumorigenesis in a kinase-inhibitor sensitive manner (Wu, 2013; Arai, 2013; Seo, 2012; reviewed in Parker, 2014).

References

Burke D, Wilkes D, Blundell TL & Malcolm S (1998). Fibroblast growth factor receptors: lessons from the genes. Trends Biochem Sci, 23, 59-62.

Webster MK & Donoghue DJ (1997). FGFR activation in skeletal disorders: too much of a good thing. Trends Genet, 13, 178-82.

Cunningham ML, Seto ML, Ratisoontorn C, Heike CL & Hing AV (2007). Syndromic craniosynostosis: from history to hydrogen bonds. Orthod Craniofac Res, 10, 67-81.

Dutt A, Salvesen HB, Chen TH, Ramos AH, Onofrio RC, Hatton C, ... Greulich H (2008). Drug-sensitive FGFR2 mutations in endometrial carcinoma. Proc Natl Acad Sci U S A, 105, 8713-7.

Pollock PM, Gartside MG, Dejeza LC, Powell MA, Mallon MA, Davies H, ... Goodfellow PJ (2007). Frequent activating FGFR2 mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes. Oncogene, 26, 7158-62.

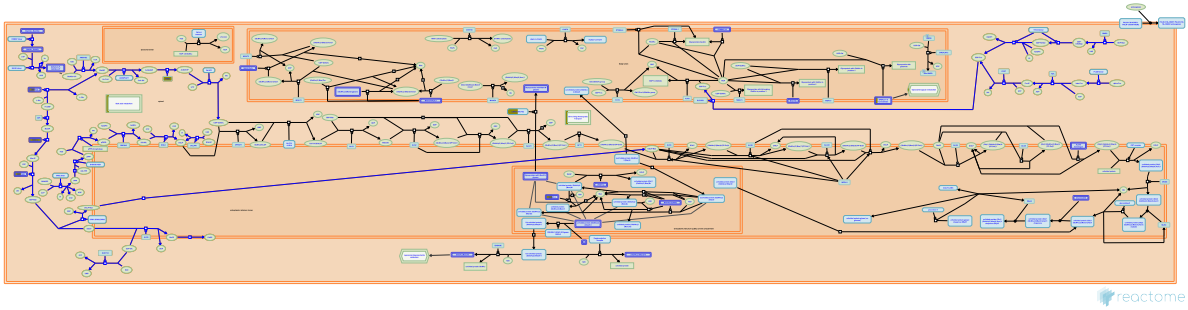
Edit history

Date	Action	Author
2011-10-27	Created	Rothfels K
2012-02-10	Authored	Rothfels K
2012-05-15	Reviewed	Ezzat S
2012-05-16	Edited	Rothfels K
2016-01-09	Revised	Rothfels K
2016-01-22	Modified	Rothfels K

Entities found in this pathway (1)

Input	UniProt Id
FGFR2	P21802, P21802-1, P21802-17, P21802-18, P21802-3, P21802-5

11. Synthesis of substrates in N-glycan biosythesis (R-HSA-446219)



Reactions for the synthesis of the small nucleotide-linked sugar substrates that are used in the synthesis of the N-glycan precursor and in the later steps of glycosylation are annotated here.

All these nucleotide-linked sugar donors are synthesized in the cytosol; however, to participate in the later reactions of N-glycan precursor biosynthesis (when the glycan is oriented toward the lumen of the endoplasmic reticulum (ER)), these substrates must be attached to a dolichyl-phosphate molecule and then flipped toward the luminal side of the ER, through a mechanism which is still not known but which involves a different protein than the one that mediates the flipping of the LLO itself (Sanyal et al. 2008). Two of the genes encoding enzymes involved in these reactions, MPI and PMM2, are known to be associated with Congenital Disorders of Glycosylation (CDG) diseases of type I. Of these, CDG-Ia, associated with defects in PMM2, is the most frequent CDG disease reported.

References

Sanyal S, Frank CG & Menon AK (2008). Distinct flippases translocate glycerophospholipids and oligosaccharide diphosphate dolichols across the endoplasmic reticulum. Biochemistry, 47, 7937-46.

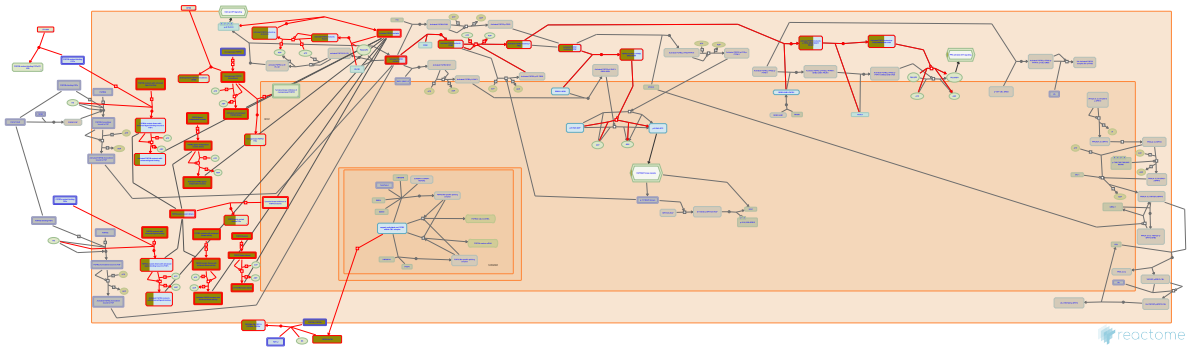
Edit history

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
2021-05-22	Modified	Shorser S

Entities found in this pathway (8)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
GFPT1	Q06210	GMPPB	Q9Y5P6	GNE	Q9Y223
NANS	Q9NR45	PGM3	O95394	PMM2	O15305, Q92871
SLC35A1	P78382	ST6GALNAC1	Q9NSC7		

12. Signaling by FGFR2 in disease (R-HSA-5655253)



Diseases: cancer, bone development disease.

The FGFR2 gene has been shown to be subject to activating mutations and gene amplification leading to a variety of proliferative and developmental disorders depending on whether these events occur in the germline or arise somatically. Activating FGFR2 mutations in the germline give rise to a range of craniosynostotic conditions including Pfeiffer, Apert, Jackson-Weiss, Crouzon and Beare-Stevensen Cutis Gyrata syndromes. These autosomal dominant skeletal disorders are characterized by premature fusion of several sutures in the skull, and in some cases also involve syndactyly (abnormal bone fusions in the hands and feet) (reviewed in Webster and Donoghue, 1997; Burke, 1998; Cunningham, 2007).

Activating FGFR2 mutations arising somatically have been linked to the development of gastric and endometrial cancers (reviewed in Greulich and Pollock, 2011; Wesche, 2011). Many of these mutations are similar or identical to those that contribute to the autosomal disorders described above. Notably, loss-of-function mutations in FGFR2 have also been recently described in melanoma (Gartside, 2009). FGFR2 may also contribute to tumorigenesis through overexpression, as FGFR2 has been identified as a target of gene amplification in gastric and breast cancers (Kunii, 2008; Takeda, 2007).

References

Webster MK & Donoghue DJ (1997). FGFR activation in skeletal disorders: too much of a good thing. Trends Genet, 13, 178-82.

Burke D, Wilkes D, Blundell TL & Malcolm S (1998). Fibroblast growth factor receptors: lessons from the genes. Trends Biochem Sci, 23, 59-62.

Cunningham ML, Seto ML, Ratisoontorn C, Heike CL & Hing AV (2007). Syndromic craniosynostosis: from history to hydrogen bonds. Orthod Craniofac Res, 10, 67-81.

Greulich H & Pollock PM (2011). Targeting mutant fibroblast growth factor receptors in cancer. Trends Mol Med, 17, 283-92.

Wesche J, Haglund K & Haugsten EM (2011). Fibroblast growth factors and their receptors in cancer. Biochem J, 437, 199-213.

Edit history

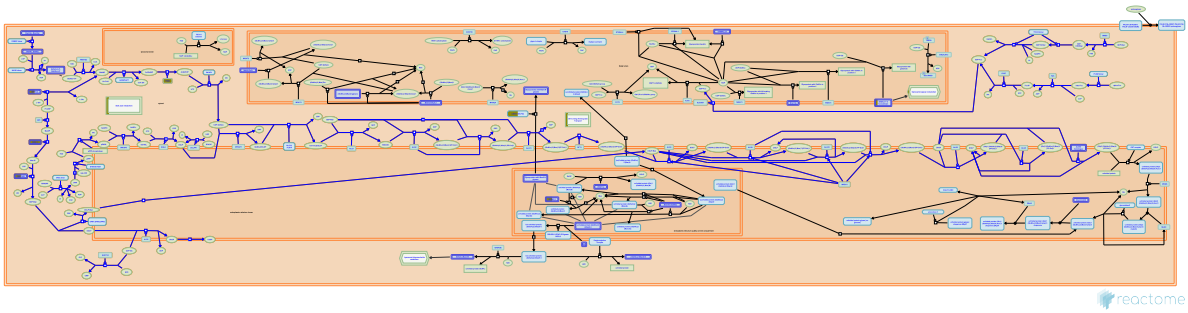
Date	Action	Author
2012-05-15	Reviewed	Ezzat S
2014-11-20	Authored	Rothfels K

Date	Action	Author
2014-12-05	Edited	Rothfels K
2014-12-05	Created	Rothfels K
2015-05-08	Modified	Rothfels K

Entities found in this pathway (1)

Input	UniProt Id
FGFR2	P21802, P21802-1, P21802-17, P21802-18, P21802-3, P21802-5

13. Biosynthesis of the N-glycan precursor (dolichol lipid-linked oligosaccharide, LLO) and transfer to a nascent protein (R-HSA-446193)



N-linked glycosylation commences with the 14-step synthesis of a dolichol lipid-linked oligosaccharide (LLO) consisting of 14 sugars (2 core GlcNAcs, 9 mannoses and 3 terminal GlcNAcs). This pathway is highly conserved in eukaryotes, and a closely related pathway is found in many eubacteria and Archaea. Mutations in the genes associated with N-glycan precursor synthesis lead to a diverse group of disorders collectively known as Congenital Disorders of Glycosylation (type I and II) (Sparks et al. 1993). The phenotypes of these disorders reflect the important role that N-glycosylation has during development, controlling the folding and the properties of proteins in the secretory pathway, and proteins that mediate cell-to-cell interactions or timing of development.

References

Sparks SE, Krasnewich DM, Pagon RA, Bird TC, Dolan CR & Stephens K (1993). *Congenital Disorders of Glycosylation Overview* .

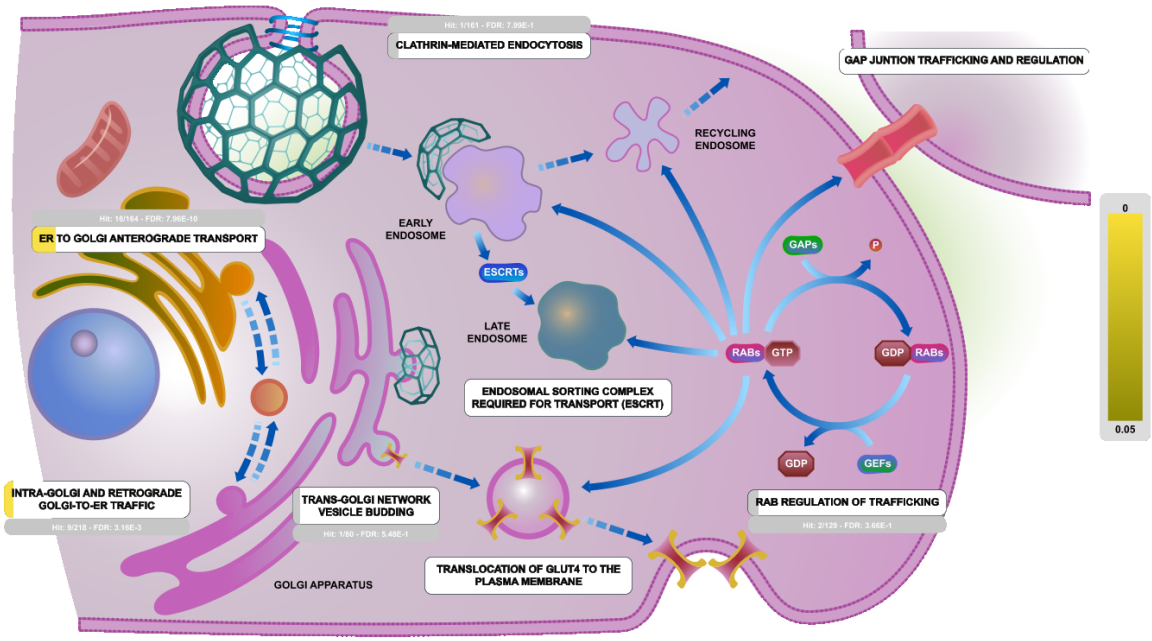
Edit history

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
2021-05-22	Modified	Shorser S

Entities found in this pathway (8)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
GFPT1	Q06210	GMPPB	Q9Y5P6	GNE	Q9Y223
NANS	Q9NR45	PGM3	O95394	PMM2	O15305, Q92871
SLC35A1	P78382	ST6GALNAC1	Q9NSC7		

14. Membrane Trafficking (R-HSA-199991)



The secretory membrane system allows a cell to regulate delivery of newly synthesized proteins, carbohydrates, and lipids to the cell surface, a necessity for growth and homeostasis. The system is made up of distinct organelles, including the endoplasmic reticulum (ER), Golgi complex, plasma membrane, and tubulovesicular transport intermediates. These organelles mediate intracellular membrane transport between themselves and the cell surface. Membrane traffic within this system flows along highly organized directional routes. Secretory cargo is synthesized and assembled in the ER and then transported to the Golgi complex for further processing and maturation. Upon arrival at the trans Golgi network (TGN), the cargo is sorted and packaged into post-Golgi carriers that move through the cytoplasm to fuse with the cell surface. This directional membrane flow is balanced by retrieval pathways that bring membrane and selected proteins back to the compartment of origin.

References

Lippincott-Schwartz J, Roberts TH & Hirschberg K (2000). Secretory protein trafficking and organelle dynamics in living cells. Annu Rev Cell Dev Biol, 16, 557-89.

Edit history

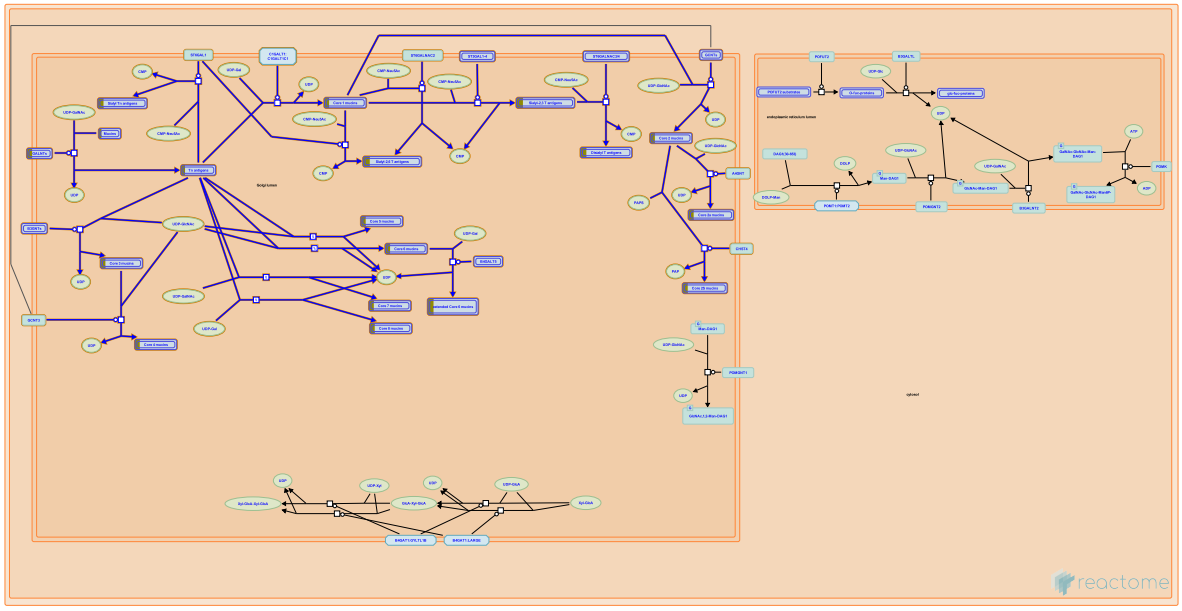
Date	Action	Author
2007-07-14	Created	Gillespie ME
2021-05-22	Modified	Shorser S

Entities found in this pathway (16)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3, Q9NP61	ARL1	P40616	COG3	Q96JB2
COPB2	P35606	GOLGA2	Q08379	GOLGB1	Q14789
KDELR2	P24390, P33947	KDELR3	O43731	LMAN1	P49257, Q9HAT1
MIA3	Q5JRA6	RAB27A	P51159	SEC16A	O15027

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
SEC24D	O94855	SYTL1	Q8IYJ3	TMED3	Q9Y3Q3
USO1	O60763				

15. O-linked glycosylation of mucins (R-HSA-913709)



Mucins are a family of high molecular weight, heavily glycosylated proteins (glycoconjugates) produced by epithelial tissues in most metazoa. Mucins' key characteristic is their ability to form gels; therefore they are a key component in most gel-like secretions, serving functions from lubrication to cell signalling to forming chemical barriers. To date, there are approximately 20 genes that express mucins. Mature mucins are composed of two distinct regions:

(1) The amino- and carboxy-terminal regions are very lightly glycosylated, but rich in cysteines. The cysteine residues participate in establishing disulfide linkages within and among mucin monomers.

(2) A large central region rich in serine, threonine and proline residues called the variable number of tandem repeat (VNTR) region which can become heavily O-glycosylated with hundreds of O-GalNAc glycans.

N-acetyl-galactosamine (GalNAc) is the first glycan to be attached, forming the simplest mucin O-glycan. After this, several different pathways are possible generating "core" structures. Four core structures are commonly formed, several others are possible but infrequent. O-linked glycans are often capped by the addition of a sialic acid residue, terminating the addition of any more O-glycans (Brockhausen et al, 2009; Tarp and Clausen, 2008).

References

Tarp MA & Clausen H (2008). Mucin-type O-glycosylation and its potential use in drug and vaccine development. Biochim Biophys Acta, 1780, 546-63.

Brockhausen I, Schachter H, Stanley P, Stanley P, Varki A, Cummings RD, ... Etzler ME (2009). *O-GalNAc Glycans* .

Edit history

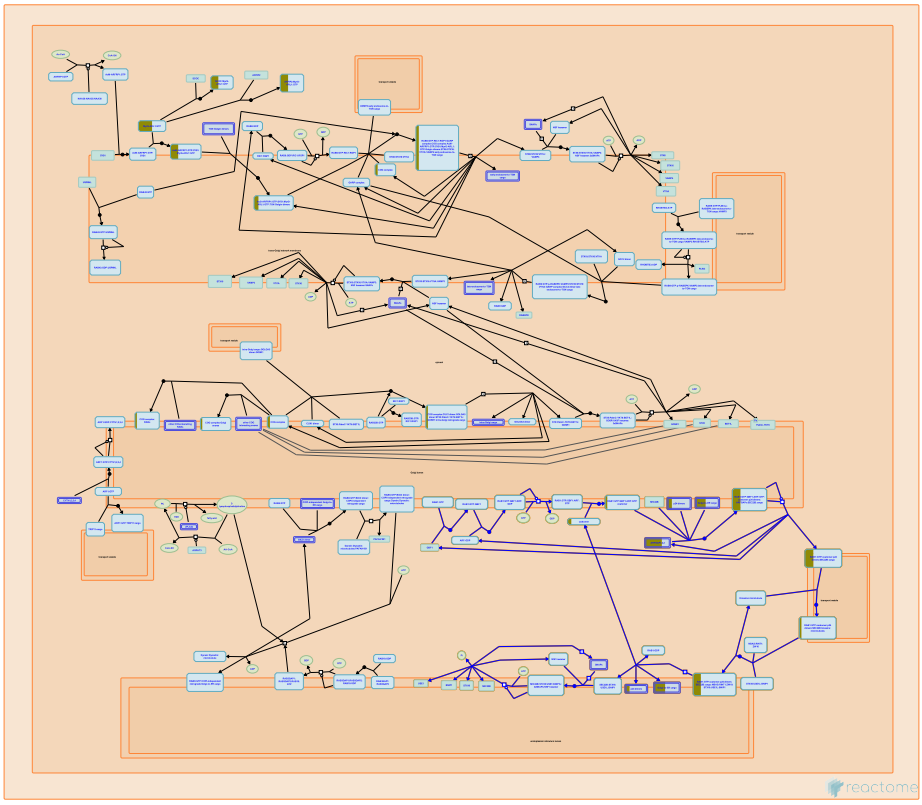
Date	Action	Author
2010-07-19	Edited	Jassal B
2010-07-19	Authored	Jassal B

Date	Action	Author
2010-07-19	Created	Jassal B
2011-11-04	Reviewed	Ferrer A
2021-05-22	Modified	Shorser S

Entities found in this pathway (6)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
GALNT12	Q8IXK2	GALNT5	Q7Z7M9	GALNT7	Q86SF2
GALNT8	Q9NY28	MUC2	Q02817	MUC4	Q99102

16. COPI-dependent Golgi-to-ER retrograde traffic (R-HSA-6811434)



Retrograde traffic from the cis-Golgi to the ERGIC or the ER is mediated in part by microtubule-directed COPI-coated vesicles (Letourneur et al, 1994; Shima et al, 1999; Spang et al, 1998; reviewed in Lord et al, 2013; Spang et al, 2013). These assemble at the cis side of the Golgi in a GBF-dependent fashion and are tethered at the ER by the ER-specific SNAREs and by the conserved NRZ multisubunit tethering complex, known as DSL in yeast (reviewed in Tagaya et al, 2014; Hong and Lev, 2014). Typical cargo of these retrograde vesicles includes 'escaped' ER chaperone proteins, which are recycled back to the ER for reuse by virtue of their interaction with the Golgi localized KDEL receptors (reviewed in Capitani and Sallese, 2009; Cancino et al, 2013).

References

Letourneur F, Gaynor EC, Hennecke S, Démollière C, Duden R, Emr SD, ... Cosson P (1994). Coatomer is essential for retrieval of dilysine-tagged proteins to the endoplasmic reticulum. Cell , 79, 1199-207.

Shima DT, Scales SJ, Kreis TE & Pepperkok R (1999). Segregation of COPI-rich and anterograde-cargo-rich domains in endoplasmic-reticulum-to-Golgi transport complexes. Curr. Biol., 9, 821-4 .

Spang A & Schekman R (1998). Reconstitution of retrograde transport from the Golgi to the ER in vitro. J. Cell Biol., 143, 589-99.

Lord C, Ferro-Novick S & Miller EA (2013). The highly conserved COPII coat complex sorts cargo from the endoplasmic reticulum and targets it to the golgi. Cold Spring Harb Perspect Biol, 5.

Spang A (2013). Retrograde traffic from the Golgi to the endoplasmic reticulum. Cold Spring Harb Perspect Biol, 5.

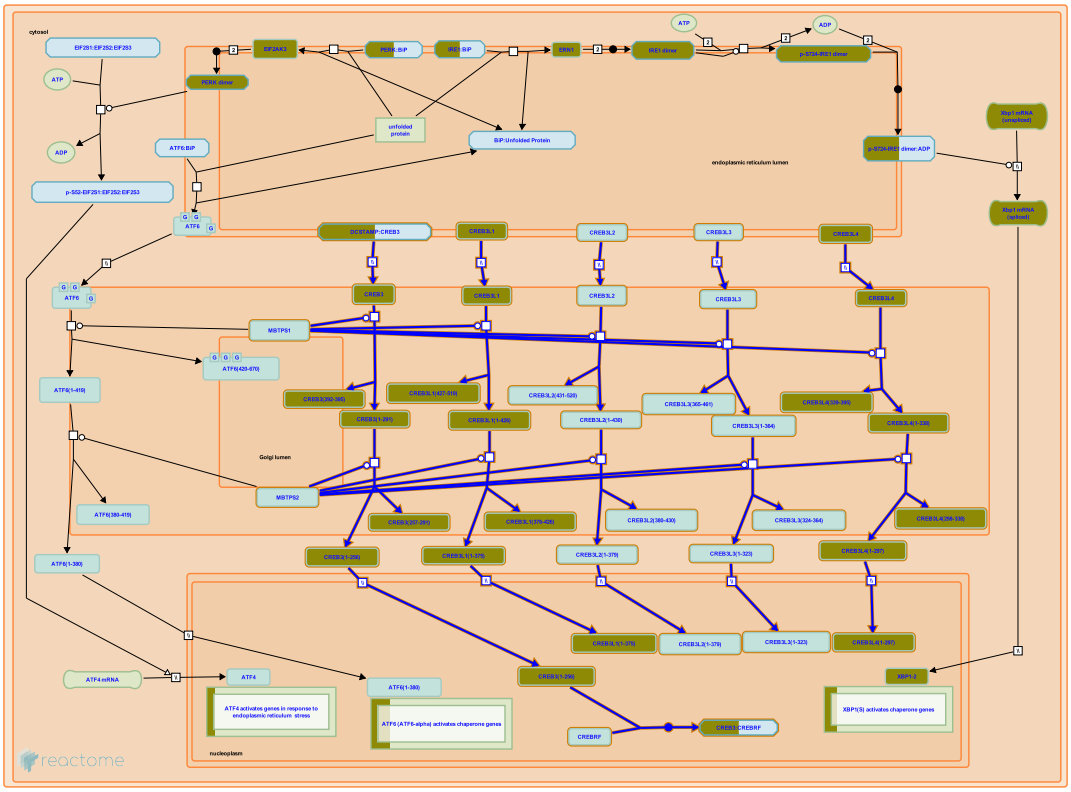
Edit history

Date	Action	Author
2015-11-09	Edited	Rothfels K
2015-11-09	Authored	Rothfels K
2015-11-19	Created	Rothfels K
2016-02-02	Reviewed	Gillespie ME
2021-05-22	Modified	Shorser S

Entities found in this pathway (5)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3, Q9NP61	COPB2	P35606	KDELR2	P24390, P33947
KDELR3	O43731	TMED3	Q9Y3Q3		

17. CREB3 factors activate genes (R-HSA-8874211)



Members of the CREB3 family (also known as the OASIS family) are tissue-specific proteins that each contain a transcription activation domain, a basic leucine zipper (bZIP) domain that promotes dimerization and DNA binding, and a transmembrane domain that anchors the protein to the membrane of the endoplasmic reticulum (ER) (reviewed in Asada et al. 2011, Chan et al. 2011, Kondo et al. 2011, Fox and Andrew 2015). The family includes CREB3 (LUMAN), CREB3L1 (OASIS), CREB3L2 (BBF2H7, Tisp40), CREB3L3 (CREB-H), and CREB3L4 (CREB4). Activation of the proteins occurs when they transit from the ER to the Golgi and are cleaved sequentially by the Golgi resident proteases MBTPS1 (S1P) and MBTPS2 (S2P), a process known as regulated intramembrane proteolysis that releases the cytoplasmic region of the protein containing the transcription activation domain and the bZIP domain. This protein fragment then transits from the cytosol to the nucleus where it activates transcription of target genes. CREB3L1, CREB3L2, and CREB3L3 are activated by ER stress, although the mechanisms that cause the transit of the CREB3 proteins are not fully characterized. Unlike the ATF6 factors, CREB3 proteins do not appear to interact with HSPA5 (BiP) and therefore do not appear to sense unfolded proteins by dissociation of HSPA5 when HSPA5 binds the unfolded proteins.

References

Kondo S, Saito A, Asada R, Kanemoto S & Imaizumi K (2011). Physiological unfolded protein response regulated by OASIS family members, transmembrane bZIP transcription factors. IUBMB Life, 63, 233-9.

Asada R, Kanemoto S, Kondo S, Saito A & Imaizumi K (2011). The signalling from endoplasmic reticulum-resident bZIP transcription factors involved in diverse cellular physiology. J. Biochem., 149, 507-18.

Fox RM & Andrew DJ (2015). Transcriptional regulation of secretory capacity by bZip transcription factors. Front Biol (Beijing), 10, 28-51.

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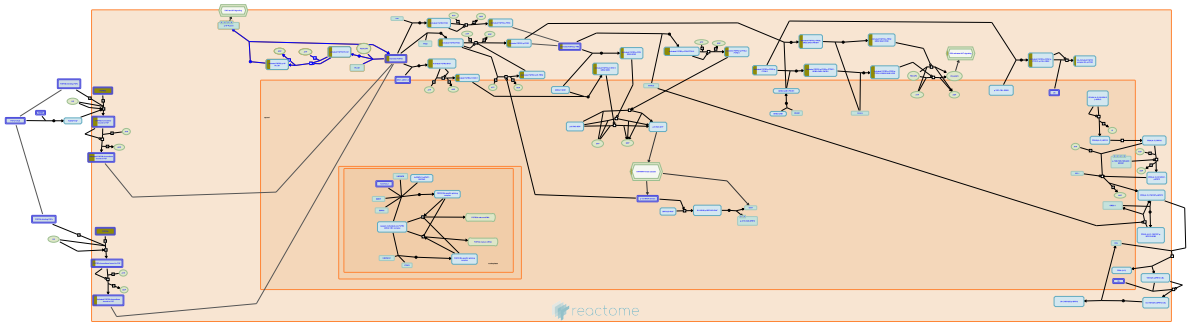
Edit history

Date	Action	Author
2016-05-21	Edited	May B
2016-05-21	Authored	May B
2016-05-21	Created	May B
2017-02-25	Reviewed	Schröder M
2021-05-22	Modified	Shorser S

Entities found in this pathway (2)

Input	UniProt Id	Input	UniProt Id
CREB3L1	Q96BA8	CREB3L4	O43889, Q8TEY5

18. Phospholipase C-mediated cascade; FGFR2 (R-HSA-5654221)



Cellular compartments: plasma membrane.

Phospholipase C-gamma (PLC-gamma) is a substrate of the fibroblast growth factor receptor (FGFR) and other receptors with tyrosine kinase activity. It is known that the src homology region 2 (SH2 domain) of PLC-gamma and of other signaling molecules (such as GTPase-activating protein and phosphatidylinositol 3-kinase-associated p85) direct their binding toward autophosphorylated tyrosine residues of the FGFR. Recruitment of PLC-gamma results in its phosphorylation and activation by the receptor. Activated PLC-gamma hydrolyzes phosphatidyl inositol[4,5] P2 to form the second messengers diacylglycerol (DAG) and Ins [1,4,5]P3, which stimulate calcium release and activation of calcium/calmodulin dependent kinases.

References

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Eswarakumar VP, Lax I & Schlessinger J (2005). Cellular signaling by fibroblast growth factor receptors. Cytokine Growth Factor Rev, 16, 139-49.

Mohammadi M, Honegger AM, Rotin D, Fischer R, Bellot F, Li W, ... Schlessinger J (1991). A tyrosine-phosphorylated carboxy-terminal peptide of the fibroblast growth factor receptor (Flg) is a binding site for the SH2 domain of phospholipase C-gamma 1. Mol Cell Biol, 11, 5068-78.

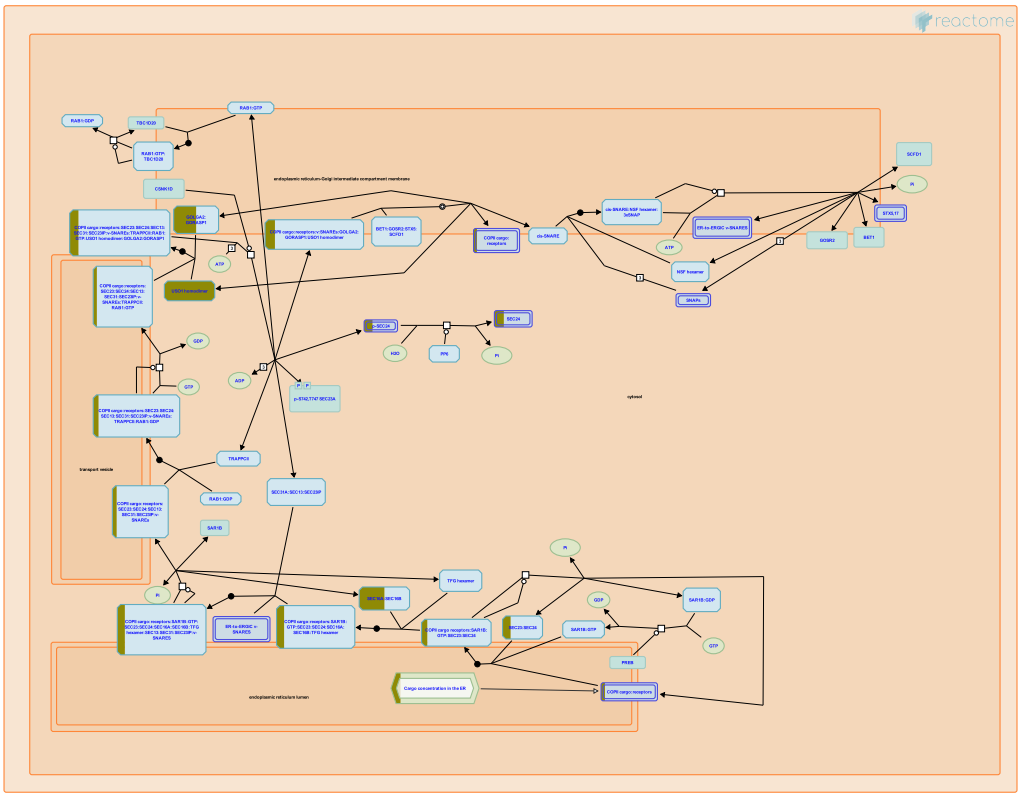
Edit history

Date	Action	Author
2007-01-10	Authored	de Bono B
2007-02-07	Reviewed	Mohammadi M
2010-02-03	Edited	Jupe S
2014-12-04	Created	Rothfels K
2021-05-21	Modified	Shorser S

Entities found in this pathway (1)

Input	UniProt Id
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5

19. COPII-mediated vesicle transport (R-HSA-204005)



COPII components (known as Sec13p, Sec23p, Sec24p, Sec31p, and Sar1p in yeast) traffic cargo from the endoplasmic reticulum to the ER-Golgi intermediate compartment (ERGIC). COPII-coated vesicles were originally discovered in the yeast Saccharomyces cerevisiae using genetic approaches coupled with a cell-free assay. The mammalian counterpart of this pathway is represented here. Newly synthesized proteins destined for secretion are sorted into COPII-coated vesicles at specialized regions of the ER. These vesicles leave the ER, become uncoated and subsequently fuse with the ERGIC membrane.

References

Kirchhausen Tomas (2000). Three ways to make a vesicle. Nat Rev Mol Cell Biol, 1, 187-98.

Sato K & Nakano A (2007). Mechanisms of COPII vesicle formation and protein sorting. FEBS Lett, 581, 2076-82.

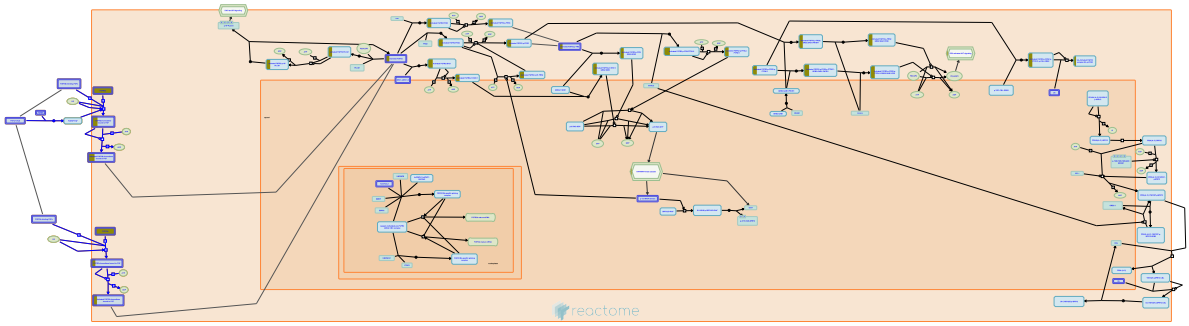
Edit history

Date	Action	Author
2007-07-14	Authored	Gillespie ME
2007-11-22	Edited	Gillespie ME
2007-11-22	Created	Gillespie ME
2010-11-18	Reviewed	Gagneux P
2015-04-18	Revised	Rothfels K
2015-08-18	Revised	Gillespie ME
2021-05-31	Modified	Shorser S

Entities found in this pathway (5)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
GOLGA2	Q08379	LMAN1	P49257, Q9HAT1	SEC16A	O15027
SEC24D	O94855	USO1	O60763		

20. FGFR2 ligand binding and activation (R-HSA-190241)



Dominant mutations in the fibroblast growth factor receptor 2 (FGFR2) gene have been identified as causes of four phenotypically distinct craniosynostosis syndromes, including Crouzon, Jackson-Weiss, Pfeiffer, and Apert syndromes. FGFR2 binds a number of different FGFs preferentially, as illustrated in this pathway.

FGFR is probably activated by NCAM very differently from the way by which it is activated by FGFs, reflecting the different conditions for NCAM-FGFR and FGF-FGFR interactions. The affinity of FGF for FGFR is approximately 10e6 times higher than that of NCAM for FGFR. Moreover, in the brain NCAM is constantly present on the cell surface at a much higher (micromolar) concentration than FGFs, which only appear transiently in the extracellular environment in the nanomolar range.

References

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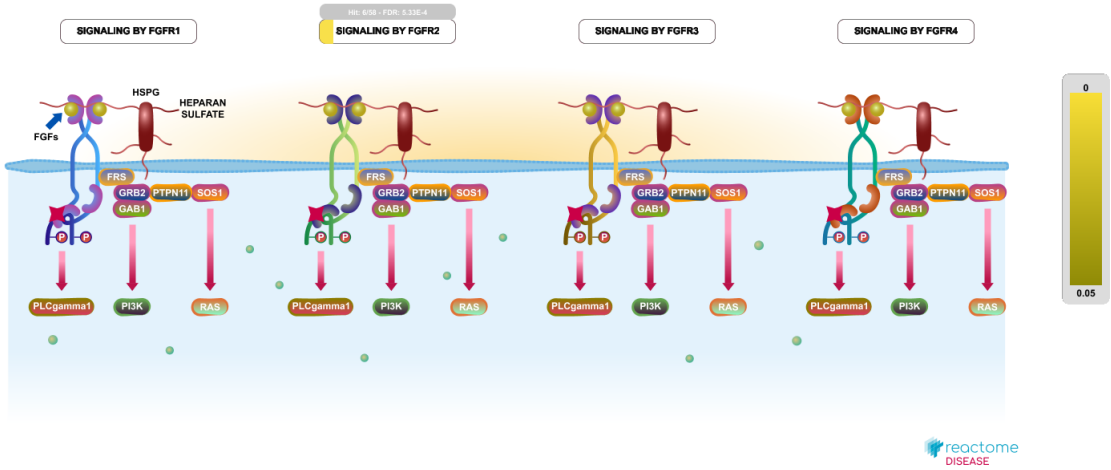
Edit history

Date	Action	Author
2006-12-18	Created	de Bono B
2007-01-10	Authored	de Bono B
2007-02-07	Reviewed	Mohammadi M
2007-02-11	Edited	D'Eustachio P, de Bono B
2021-05-21	Modified	Shorser S

Entities found in this pathway (1)

Input	UniProt Id
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5

21. Signaling by FGFR in disease (R-HSA-1226099)



Diseases: bone development disease, cancer.

A number of skeletal and developmental diseases have been shown to arise as a result of mutations in the FGFR1, 2 and 3 genes. These include dwarfism syndromes (achondroplasia, hypochondroplasia and the neonatal lethal disorders thanatophoric dysplasia I and II), as well as craniosynostosis disorders such as Pfeiffer, Apert, Crouzon, Jackson-Weiss and Muenke syndromes (reviewed in Webster and Donoghue 1997; Burke, 1998, Cunningham, 2007; Harada, 2009). These mutations fall into four general regions of the receptor: a) the immunoglobulin (Ig)-like domain II-III linker region, b) the alternatively spliced second half of the Ig III domain, c) the transmembrane domain and d) the tyrosine kinase domain (reviewed in Webster and Donoghue, 1997). With the exception of mutations in class b), which affect only the relevant splice variant, these mutations may be present in either the 'b' or 'c' isoforms. These activating mutations affect FGFR function by altering or expanding the ligand-binding range of the receptors (see for instance Ibrahimi, 2004a), by promoting ligand-independent dimerization (for instance, Galvin,1996; Neilson and Friesel, 1996; d'Avis,1998) or by increasing the activity of the kinase domain (for instance, Webster, 1996; Naski, 1996; Tavormina, 1999; Bellus, 2000). Thus, a number of the point mutations found in FGFR receptors alter their activity without altering their intrinsic kinase activity. Many of the mutations that promote constitutive dimerization do so by creating or removing cysteine residues; the presence of an unpaired cysteine in the receptor is believed to promote dimerization through the formation of intramolecular disulphide bonds (Galvin, 1996; Robertson, 1998). Paralogous mutations at equivalent positions have been identified in more than one FGF receptor, sometimes giving rise to different diseases. For instance, mutation of the highly conserved FGFR2 Ser252-Pro253 dipeptide in the region between the second and third Ig domain is responsible for virtually all cases of Apert Syndrome (Wilkie, 1995), while paralogous mutations in FGFR1 (S252R) and FGFR3 (P250R) are associated with Pfeiffer and Crouzon syndromes, respectively (Bellus, 1996). FGFR4 is unique in that mutations of this gene are not known to be associated with any developmental disorders.

Recently, many of the same activating mutations in the FGFR genes that have been characterized in skeletal and developmental disorders have begun to be identified in a range of cancers (reviewed in Turner and Gross, 2010; Greulich and Pollock, 2011; Wesche, 2011). The best established link between a somatic mutation of an FGFR and the development of cancer is in the case of FGFR3, where 50% of bladder cancers have mutations in the FGFR3 coding sequence. Of these mutations, which largely match the activating mutations seen in thanatophoric dysplasias, over half occur at a single residue (S249C) (Cappellen, 1999; van Rhijn, 2002). Activating mutations have also been identified in the coding sequences of FGFR1, 2 and 4 (for review, see Wesche, 2011)

In addition to activating point mutations, the FGFR1, 2 and 3 genes are subject to misregulation in cancer through gene amplification and translocation events, which are thought to lead to overexpression and ligand-independent dimerization (Weiss, 2010; Turner, 2010; Kunii, 2008; Takeda, 2007; Chesi, 1997; Avet-Loiseau, 1998; Ronchetti, 2001). It is important to note, however, that in each of these cases, the amplification or translocation involve large genomic regions encompassing additional genes, and the definitive roles of the FGFR genes in promoting oncogenesis has not been totally established. In the case of FGFR1, translocation events also give rise to FGFR1 fusion proteins that contain the intracellular kinase domain of the receptor fused to a dimerization domain from the partner gene. These fusions, which are expressed in a pre-leukemic myeloproliferative syndrome, dimerize constitutively based on the dimerization domain provided by the fusion partner and are constitutively active (reviewed in Jackson, 2010).

References

Webster MK & Donoghue DJ (1997). FGFR activation in skeletal disorders: too much of a good thing. Trends Genet, 13, 178-82.

Burke D, Wilkes D, Blundell TL & Malcolm S (1998). Fibroblast growth factor receptors: lessons from the genes. Trends Biochem Sci, 23, 59-62.

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Harada D, Yamanaka Y, Ueda K, Tanaka H & Seino Y (2009). FGFR3-related dwarfism and cell signaling. J Bone Miner Metab, 27, 9-15.

Galvin BD, Hart KC, Meyer AN, Webster MK & Donoghue DJ (1996). Constitutive receptor activation by Crouzon syndrome mutations in fibroblast growth factor receptor (FGFR)2 and FGFR2/Neu chimeras. Proc Natl Acad Sci U S A, 93, 7894-9.

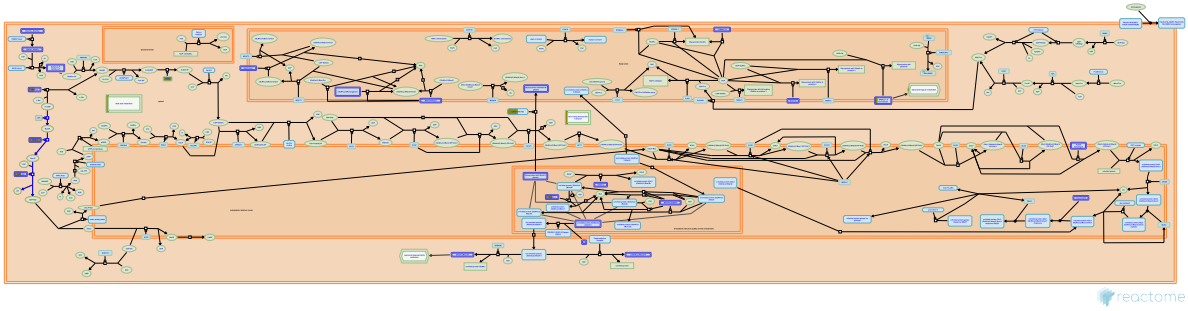
Edit history

Date	Action	Author
2011-03-09	Created	Rothfels K
2012-02-10	Authored	Rothfels K
2012-05-15	Edited	Rothfels K
2012-05-15	Reviewed	Ezzat S
2016-01-25	Reviewed	Grose RP
2021-05-04	Modified	Matthews L

Entities found in this pathway (1)

Input	UniProt Id
FGFR2	P21802, P21802-1, P21802-17, P21802-18, P21802-3, P21802-5

22. Synthesis of GDP-mannose (R-HSA-446205)



GDP-mannose is the mannose donor for the first 5 mannose addition reactions in the N-glycan precursor synthesis, and also for the synthesis of Dolichyl-phosphate-mannose involved in other mannose transfer reactions. It is synthesized from fructose 6-phosphate and GTP in three steps.

References

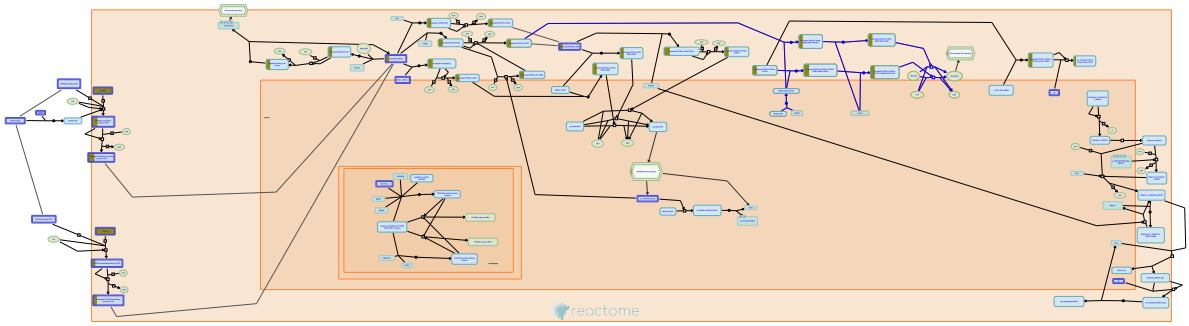
Edit history

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
2021-05-22	Modified	Shorser S

Entities found in this pathway (2)

Input	UniProt Id	Input	UniProt Id
GMPPB	Q9Y5P6	PMM2	O15305, Q92871

23. PI-3K cascade:FGFR2 (R-HSA-5654695)



The ability of growth factors to protect from apoptosis is primarily due to the activation of the AKT survival pathway. P-I-3-kinase dependent activation of PDK leads to the activation of AKT which in turn affects the activity or expression of pro-apoptotic factors, which contribute to protection from apoptosis. AKT activation also blocks the activity of GSK-3b which could lead to additional antiapoptotic signals.

References

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Kamei T, Jones SR, Chapman BM, MCGonigle KL, Dai G & Soares MJ (2002). The phosphatidylinositol 3-kinase/Akt signaling pathway modulates the endocrine differentiation of trophoblast cells. Mol Endocrinol, 16, 1469-81.

Eswarakumar VP, Lax I & Schlessinger J (2005). Cellular signaling by fibroblast growth factor receptors. Cytokine Growth Factor Rev, 16, 139-49.

Hart KC, Robertson SC, Kanemitsu MY, Meyer AN, Tynan JA & Donoghue DJ (2000). Transformation and Stat activation by derivatives of FGFR1, FGFR3, and FGFR4. Oncogene, 19, 3309-20.

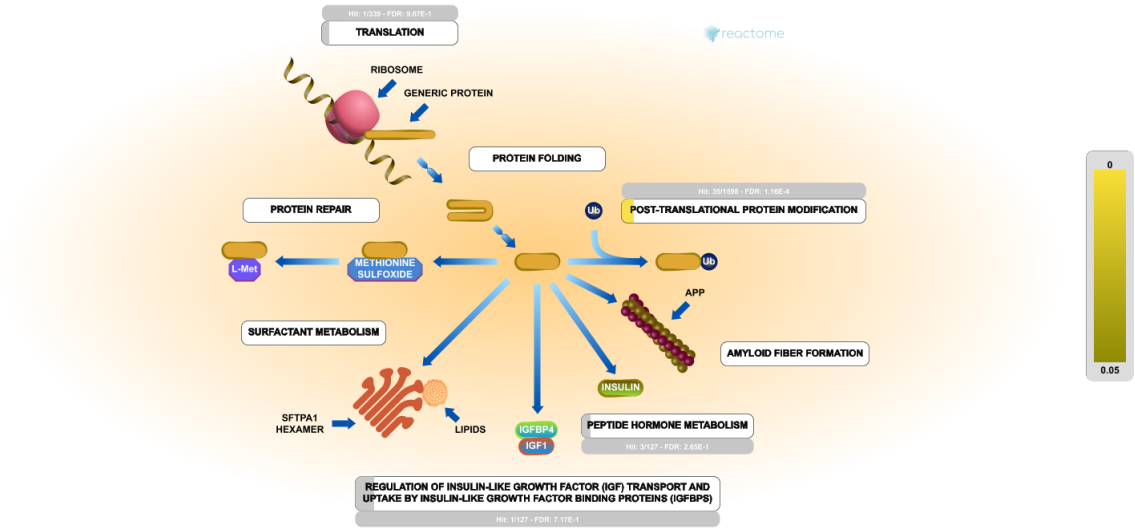
Edit history

Date	Action	Author
2007-01-10	Authored	de Bono B
2007-02-07	Reviewed	Mohammadi M
2010-02-03	Edited	Jupe S
2014-12-04	Created	Rothfels K
2021-05-31	Modified	Shorser S

Entities found in this pathway (1)

Input	UniProt Id
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5

24. Metabolism of proteins (R-HSA-392499)



Metabolism of proteins, as annotated here, covers the full life cycle of a protein from its synthesis to its posttranslational modification and degradation, at various levels of specificity. Protein synthesis is accomplished through the process of Translation of an mRNA sequence into a polypeptide chain. Protein folding is achieved through the function of molecular chaperones which recognize and associate with proteins in their non-native state and facilitate their folding by stabilizing the conformation of productive folding intermediates (Young et al. 2004). Following translation, many newly formed proteins undergo Post-translational protein modification, essentially irreversible covalent modifications critical for their mature locations and functions (Knorre et al. 2009), including gamma carboxylation, synthesis of GPI-anchored proteins, asparagine N-linked glycosylation, O-glycosylation, SUMOylation, ubiquitination, deubiquitination, RAB geranylgeranylation, methylation, carboxyterminal post-translational modifications, neddylation, and phosphorylation. Peptide hormones are synthesized as parts of larger precursor proteins whose cleavage in the secretory system (endoplasmic reticulum, Golgi apparatus, secretory granules) is annotated in Peptide hormone metabolism. After secretion, peptide hormones are modified and degraded by extracellular proteases (Chertow, 1981 PMID:6117463). Protein repair enables the reversal of damage to some amino acid side chains caused by reactive oxygen species. Pulmonary surfactants are lipids and proteins that are secreted by the alveolar cells of the lung that decrease surface tension at the air/liquid interface within the alveoli to maintain the stability of pulmonary tissue (Agassandian and Mallampalli 2013). Nuclear regulation, transport, metabolism, reutilization, and degradation of surfactant are described in the Surfactant metabolism pathway. Amyloid fiber formation, the accumulation of mostly extracellular deposits of fibrillar proteins, is associated with tissue damage observed in numerous diseases including late phase heart failure (cardiomyopathy) and neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's.

References

Edit history

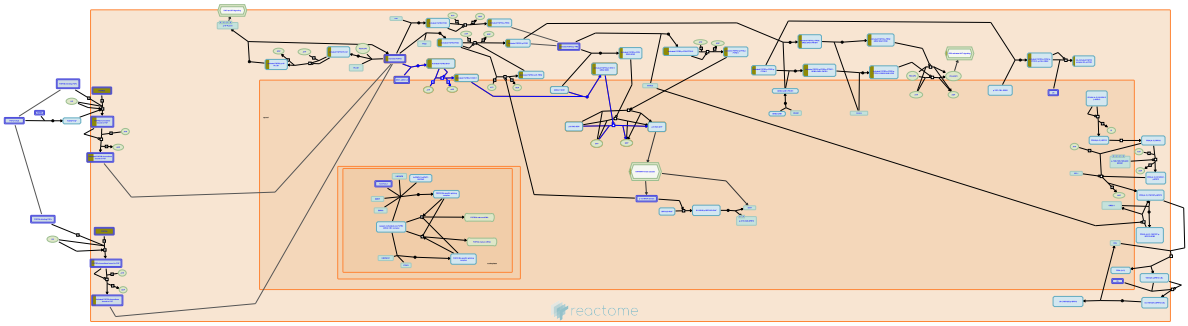
Date	Action	Author
2009-03-04	Edited	Matthews L

Date	Action	Author
2009-03-05	Authored	Matthews L
2009-03-05	Created	Matthews L
2021-05-22	Modified	Shorser S

Entities found in this pathway (34)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARFGAP1	Q8N6T3, Q9NP61	ATOH1	P61086	B4GALT4	O60513
COG3	Q96JB2	COPB2	P35606	EDEM3	Q9BZQ6
GALNT12	Q8IXK2	GALNT5	Q7Z7M9	GALNT7	Q86SF2
GALNT8	Q9NY28	GFPT1	Q06210	GMPPB	Q9Y5P6
GNE	Q9Y223	GOLGA2	Q08379	GOLGB1	Q14789
KDELR2	P24390, P33947	KDELR3	O43731	KLF4	O43474
LMAN1	P49257, Q9HAT1	MIA3	Q5JRA6	MUC2	Q02817
MUC4	Q99102	NANS	Q9NR45	PGM3	O95394
PMM2	O15305, Q92871	RAB27A	P51159	SEC16A	O15027
SEC24D	O94855	SLC30A7	Q8NEW0	SLC35A1	P78382
SSR3	Q9UNL2	ST6GALNAC1	Q9NSC7	TMED3	Q9Y3Q3
USO1	O60763				

25. SHC-mediated cascade:FGFR2 (R-HSA-5654699)



Cellular compartments: plasma membrane.

The exact role of SHC1 in FGFR signaling remains unclear. Numerous studies have shown that the p46 and p52 isoforms of SHC1 are phosphorylated in response to FGF stimulation, but direct interaction with the receptor has not been demonstrated. Co-precipitation of p46 and p52 with the FGFR2 IIIc receptor has been reported, but this interaction is thought to be indirect, possibly mediated by SRC. Consistent with this, co-precipitation of SHC1 and FGFR1 IIIc is seen in mammalian cells expressing v-SRC. The p66 isoform of SHC1 has also been co-precipitated with FGFR3, but this occurs independently of receptor stimulation, and the p66 isoform not been shown to undergo FGF-dependent phosphorylation. SHC1 has been shown to associate with GRB2 and SOS1 in response to FGF stimulation, suggesting that the recruitment of SHC1 may contribute to activation of the MAPK cascade downstream of FGFR.

References

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Eswarakumar VP, Lax I & Schlessinger J (2005). Cellular signaling by fibroblast growth factor receptors. Cytokine Growth Factor Rev, 16, 139-49.

Schüller AC, Ahmed Z, Levitt JA, Suen KM, Suhling K & Ladbury JE (2008). Indirect recruitment of the signalling adaptor Shc to the fibroblast growth factor receptor 2 (FGFR2). Biochem J, 416, 189-99.

Kanai M, Goke M, Tsunekawa S & Podolsky DK (1997). Signal transduction pathway of human fibroblast growth factor receptor 3. Identification of a novel 66-kDa phosphoprotein. J Biol Chem, 272, 6621-8.

Wang JK, Gao G & Goldfarb M (1994). Fibroblast growth factor receptors have different signaling and mitogenic potentials. Mol Cell Biol, 14, 181-8.

Edit history

Date	Action	Author
2007-01-10	Authored	de Bono B
2007-02-07	Reviewed	Mohammadi M
2010-02-03	Edited	Jupe S
2014-12-04	Created	Rothfels K
2021-05-31	Modified	Shorser S

Entities found in this pathway (1)

Input	UniProt Id
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5

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 (73)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ANO7	Q6IWH7	ARFGAP1	Q8N6T3	ARL1	P40616
ATOH1	P61086	B4GALT4	O60513	CANT1	Q08380
CAPN8	A6NHC0, Q6ZSI9	CAPN9	O14815	CDC42EP5	Q6NZY7
CLCA1	A8K7I4	COG3	Q96JB2	COPB2	P35606
CRACR2A	Q9BSW2	CREB3L1	Q96BA8	CREB3L4	O43889, Q8TEY5
EDEM3	Q9BZQ6	EIF2AK3	Q9NZJ5	ENTPD8	Q5MY95
ERLEC1	Q96DZ1	ERN2	O75460	FGFR2	P21802, P21802-1, P21802-18, P21802-3, P21802-5
FOXA3	P55318	GALNT12	Q8IXK2	GALNT5	Q7Z7M9
GALNT7	Q86SF2	GALNT8	Q9NY28	GFPT1	Q06210
GMPPB	Q9Y5P6	GNE	Q9Y223	GOLGA2	Q08379
GOLGB1	Q14789	GORASP2	Q9H8Y8	HDLBP	Q00341
HERPUD1	Q15011	KCNK6	Q9Y257	KCNMA1	Q12791
KDELR2	P24390, P33947	KDELR3	O43731	KLF4	O43474
LMAN1	P49257, Q9HAT1	MB	P02144	MCF2L	O15068
MIA3	Q5JRA6	MLLT3	P42568	MUC2	Q02817
MUC4	Q99102	MXD4	Q14582	NANS	Q9NR45
PDIA5	Q14554	PGM3	O95394	PLA2G10	O15496
PMM2	O15305, Q92871	PTGER4	P35408	RAB27A	P51159
RAP1GAP	P47736	SCNN1A	P37088	SEC16A	O15027
SEC24D	O94855	SH3PXD2A	Q5TCZ1	SLC16A7	O60669
SLC2A10	O95528	SLC30A7	Q8NEW0	SLC35A1	P78382
SLC39A7	Q92504	SLC50A1	Q9BRV3	SSR3	Q9UNL2
ST6GALNAC1	Q9NSC7	SYTL1	Q8IYJ3	TFF3	Q07654
TMED3	Q9Y3Q3	USO1	O60763	WNK4	Q96J92
XBP1	P17861-2				

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
ARFGAP1	ENSG00000101199	FOXA3	ENSG00000170608	GFPT1	ENSG00000198380
HERPUD1	ENSG00000051108	KDELR3	ENSG00000100196	KLF4	ENSG00000136826
MXD4	ENSG00000123933	PDIA5	ENSG00000065485	TFF3	ENSG00000160180
XBP1	ENSG00000100219, ENST00000216037, ENST00000344347				

7. Identifiers not found

These 45 identifiers were not found neither mapped to any entity in Reactome.

AGR2	AL390719.2	BCAS1	BLCAP	C3orf52	DHX32	DNAJC10	ERGIC1
FAM107B	FAM110C	FAM174B	FAM83E	FCGBP	FRYL	HES2	HID1
LARP1B	LRRC31	MARVELD1	MLPH	PLXDC2	PODXL	PRIMPOL	REP15
SEL1L3	SGSM3	SLC12A8	SLC22A23	SLC39A11	SLC9A3R2	SMIM14	SPDEF
SPINK4	SYTL2	TACC1	TAGLN	TCEA3	TM9SF3	TMEM184A	TMEM214
TPSG1	TSPAN13	TTC39A	URAD	ZG16			