reactome

Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 84 on 12/05/2023. The web link to these results is:

https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAyMzA1MTIxNjAzMDdfMTU2MTQ%3D

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

Table of Contents

1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for Homo sapiens are available for 17 non-human species including mouse, rat, chicken, puffer fish, worm, fly, yeast, rice, and Arabidopsis. Pathways are represented by simple diagrams following an SBGN-like format.

Reactome's annotated data describe reactions possible if all annotated proteins and small molecules were present and active simultaneously in a cell. By overlaying an experimental dataset on these annotations, a user can perform a pathway over-representation analysis. By overlaying quantitative expression data or time series, a user can visualize the extent of change in affected pathways and its progression. A binomial test is used to calculate the probability shown for each result, and the p-values are corrected for the multiple testing (Benjamini–Hochberg procedure) that arises from evaluating the submitted list of identifiers against every pathway.

To learn more about our Pathway Analysis, please have a look at our relevant publications:

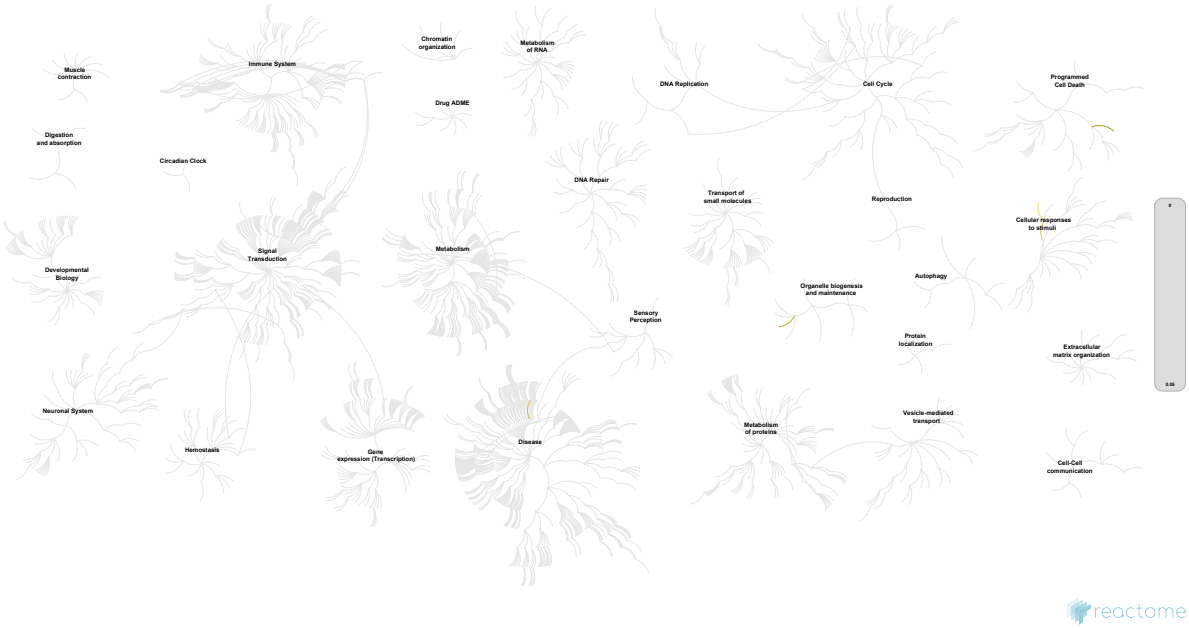
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, … D'Eustachio P (2016). The reactome pathway knowledgebase. Nucleic Acids Research, 44(D1), D481–D487. https://doi.org/10.1093/nar/gkv1351.

Fabregat A, Sidiropoulos K, Viteri G, Forner O, Marin-Garcia P, Arnau V, … Hermjakob H (2017). Reactome pathway analysis: a high-performance in-memory approach. BMC Bioinformatics, 18.

2. Properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method.
- 15 out of 41 identifiers in the sample were found in Reactome, where 299 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent.
- IntAct interactors were included to increase the analysis background. This greatly increases the size of Reactome pathways, which maximises the chances of matching your submitted identifiers to the expanded pathway, but will include interactors that have not undergone manual curation by Reactome and may include interactors that have no biological significance, or unexplained relevance.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMzA1MTIxNjAzMDdfMTU2MTQ%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.

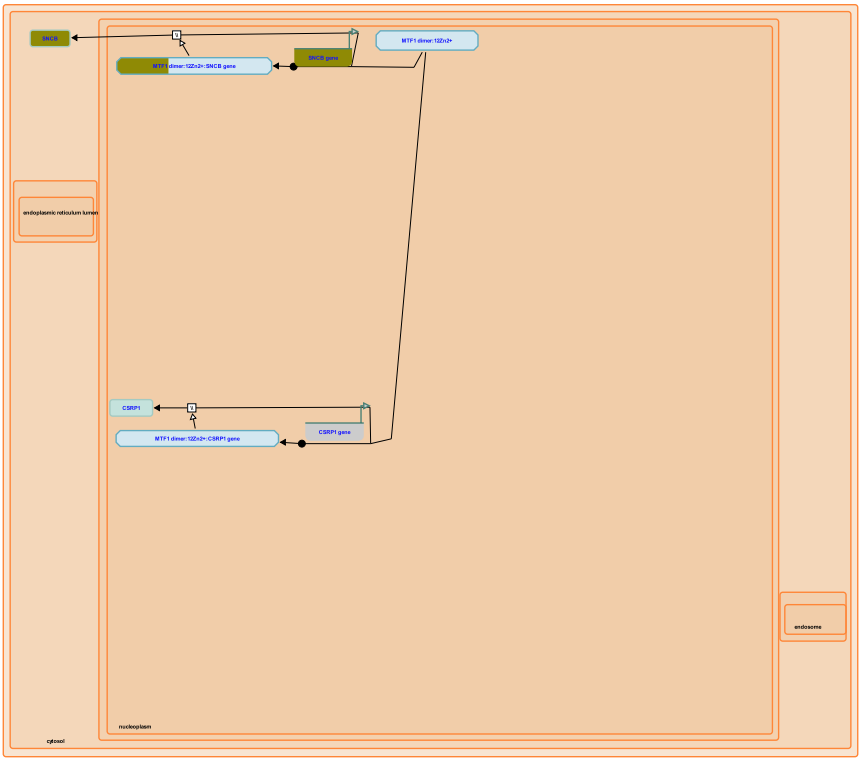
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
MTF1 activates gene expression	2 / 16	7.13e-04	7.09e-04	0.215	2 / 4	2.82e-04
Response to metal ions	2 / 71	0.003	0.013	0.538	2 / 31	0.002
Signaling by membrane-tethered fusions of PDGFRA or PDGFRB	1 / 7	3.12e-04	0.017	0.538	2 / 2	1.41e-04
Defective CHST3 causes SEDCJD	1 / 9	4.01e-04	0.021	0.538	1 / 1	7.04e-05
Trafficking of myristoylated proteins to the cilium	1 / 11	4.90e-04	0.026	0.538	4 / 8	5.64e-04
Apoptosis induced DNA fragmentation	1 / 17	7.57e-04	0.04	0.538	2 / 12	8.45e-04
Drug-mediated inhibition of MET activation	1 / 23	0.001	0.054	0.538	1 / 2	1.41e-04
Chondroitin sulfate biosynthesis	1 / 27	0.001	0.063	0.538	1 / 9	6.34e-04
VEGF binds to VEGFR leading to receptor dimerization	1 / 29	0.001	0.067	0.538	2 / 3	2.11e-04
VEGF ligand-receptor interactions	1 / 29	0.001	0.067	0.538	2 / 4	2.82e-04
Neurophilin interactions with VEGF and VEGFR	1 / 31	0.001	0.072	0.538	1 / 2	1.41e-04
MET Receptor Activation	1 / 33	0.001	0.076	0.538	1 / 5	3.52e-04
Laminin interactions	1 / 33	0.001	0.076	0.538	2 / 15	0.001
PD-1 signaling	1 / 34	0.002	0.079	0.538	5 / 5	3.52e-04
Regulation of FZD by ubiquitination	1 / 35	0.002	0.081	0.538	3 / 6	4.23e-04
SEMA3A-Plexin repulsion signaling by inhibiting Integrin adhesion	1 / 37	0.002	0.085	0.538	1 / 8	5.64e-04
Signaling by PDGFR in disease	1 / 37	0.002	0.085	0.538	2 / 24	0.002
InlB-mediated entry of Listeria monocytogenes into host cell	1 / 39	0.002	0.09	0.538	1 / 8	5.64e-04
MET activates PTPN11	1 / 43	0.002	0.098	0.538	1 / 1	7.04e-05
Collagen chain trimerization	1 / 44	0.002	0.101	0.538	1 / 28	0.002
Pyrimidine catabolism	1 / 51	0.002	0.116	0.538	2 / 17	0.001
Signal attenuation	1 / 52	0.002	0.118	0.538	2 / 7	4.93e-04
SHC1 events in EGFR signaling	1 / 53	0.002	0.12	0.538	1 / 4	2.82e-04
Erythropoietin activates RAS	1 / 54	0.002	0.122	0.538	1 / 8	5.64e-04
Diseases associated with glycosaminoglycan metabolism	1 / 55	0.002	0.124	0.538	1 / 29	0.002

* 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. MTF1 activates gene expression (R-HSA-5660489)



The MTF1:zinc complex in the nucleus binds Metal Response Elements (MREs), DNA containing the core consensus sequence 5'-TGCRCNC-3', and activates or represses transcription depending on the context of the MRE (reviewed in Laity and Andrews 2007, Jackson et al. 2008, Gunther et al. 2012, Grzywacz et al. 2015). The 6 zinc fingers of each MTF1 monomer have different affinities for zinc and evidence from the mouse homolog indicates that different concentrations of zinc, and hence different metal loads in MTF1, activate different subsets of target genes (Wang et al. 2004, Dong et al. 2015). Genes activated by MTF1 include those encoding metallothioneins, zinc transporters, and stress-response proteins (Hardyman et al. 2016).

References

Opoka W, Tyszka-Czochara M, Grzywacz A, Muszyńska B, Gdula-Argasińska J & Librowski T (2015). Metal responsive transcription factor 1 (MTF-1) regulates zinc dependent cellular processes at the molecular level. Acta Biochim. Pol., 62, 491-8.

Jackson KA, Coneyworth LJ, Valentine RA, Ford D & Mathers JC (2008). Mechanisms of mammalian zinc-regulated gene expression. Biochem. Soc. Trans., 36, 1262-6.

Wang Q, Dou Y, Dong G, Chen H & Qi M (2015). Balance between metallothionein and metal response element binding transcription factor 1 is mediated by zinc ions (review). Mol Med Rep, 11, 1582-6.

Wakeling LA, Hardyman JE, Valentine RA, Aldridge C, Tyson J, Jackson KA, ... Cockell SJ (2016). Zinc sensing by metal-responsive transcription factor 1 (MTF1) controls metallothionein and ZnT1 expression to buffer the sensitivity of the transcriptome response to zinc. Metallomics, 8, 337-43.

Andrews GK & Laity JH (2007). Understanding the mechanisms of zinc-sensing by metal-response element binding transcription factor-1 (MTF-1). Arch. Biochem. Biophys., 463, 201-10.

Edit history

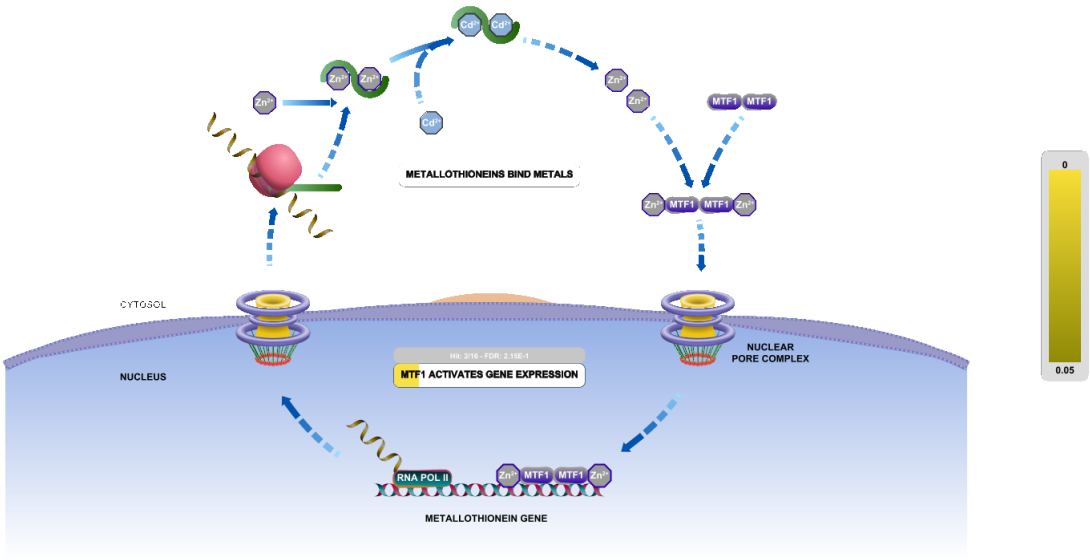
Date	Action	Author
2014-12-28	Edited	May B
2014-12-28	Authored	May B
2015-01-05	Created	May B
2017-01-27	Modified	May B
2017-01-27	Reviewed	Wang Q, Ford D

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

Input	UniProt Id
SNCB	Q16143

Input	Ensembl Id
SNCB	ENSG00000074317

2. Response to metal ions (R-HSA-5660526)



Though metals such as zinc, copper, and iron are required as cofactors for cellular enzymes they can also catalyze damaging metal substitution or unspecific redox reactions if they are not sequestered. The transcription factor MTF1 directs the major cellular response to zinc, cadmium, and copper. MTF1 activates gene expression to up-regulate genes encoding proteins, such as metallothioneins and glutamate-cysteine ligase (GCLC), involved in sequestering metals. MTF1 represses gene expression to down-regulate genes encoding transporters that import the metals into the cell (reviewed in Laity and Andrews 2007, Jackson et al. 2008, Günther et al. 2012, Dong et al. 2015). During activation MTF1 in the cytosol binds zinc ions and is translocated into the nucleus, where it binds metal response elements in the promoters of target genes. Activation of MTF1 by cadmium and copper appears to be indirect as these metals displace zinc from metallothioneins and the displaced zinc then binds MTF1.

Metallothioneins bind metals and participate in detoxifying heavy metals, storing and transporting zinc, and redox biochemistry.

References

Jackson KA, Coneyworth LJ, Valentine RA, Ford D & Mathers JC (2008). Mechanisms of mammalian zinc-regulated gene expression. Biochem. Soc. Trans., 36, 1262-6.

Wang Q, Dou Y, Dong G, Chen H & Qi M (2015). Balance between metallothionein and metal response element binding transcription factor 1 is mediated by zinc ions (review). Mol Med Rep, 11, 1582-6.

Andrews GK & Laity JH (2007). Understanding the mechanisms of zinc-sensing by metal-response element binding transcription factor-1 (MTF-1). Arch. Biochem. Biophys., 463, 201-10.

Lindert U, Günther V & Schaffner W (2012). The taste of heavy metals: gene regulation by MTF-1. Biochim. Biophys. Acta, 1823, 1416-25.

Edit history

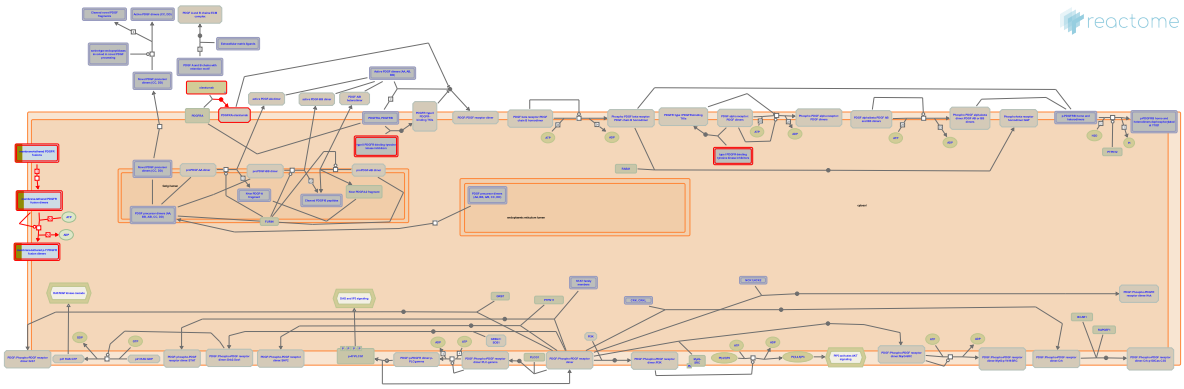
Date	Action	Author
2014-12-28	Edited	May B
2014-12-28	Authored	May B
2015-01-05	Created	May B
2015-09-19	Reviewed	Atrian S
2023-03-09	Modified	Wright A

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

Input	UniProt Id
SNCB	Q16143

Input	Ensembl Id
SNCB	ENSG00000074317

3. Signaling by membrane-tethered fusions of PDGFRA or PDGFRB (R-HSA-9673768)



Diseases: cancer.

In addition to activating missensse and in-frame deletion mutations, PDGFRA and PDGFRB are also subject to low frequency gene fusion events arising from chromosomal rearrangements. To date there are about 35 identified PDGFRA or B fusion partners, with PDGFRB being the more common partner (reviewed in Appiah-Kubi et al, 2017). Although some of the PDGF fusions proteins are cytosolic by virtue of removal of the PDGFR transmembrane region (TMD), a number of fusions retain the TMD and are linked to the plasma membrane (Hidalgo-Curtis et al, 2010; Ozawa et al, 2010; Curtis et al, 2007; Medves et al, 2010; reviewed in Appiah-Kubi et al, 2017). The most common transmembrane fusion partner of PDGFRA and PDGFRB is ETV6 (also known as TEL1), a transcriptional repressor with known ability to homodimerize (Curtis et al, 2007; Golub et al, 1994; Andrae et al, 2008; reviewed in de Braekeleer et al, 2012; Wang et al, 2016; Appiah-Kubi et al, 2017).

References

Yao X, Chen Y, Wu M, Qian H, Wang Y, Wu Y & Appiah-Kubi K (2016). The platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) are major players in oncogenesis, drug resistance, and attractive oncologic targets in cancer. Growth Factors, 34, 64-71.

De Braekeleer E, De Braekeleer M, Douet-Guilbert N, Basinko A, Le Bris MJ & Morel F (2012). ETV6 fusion genes in hematological malignancies: a review. Leuk. Res., 36, 945-61.

Betsholtz C, Andrae J & Gallini R (2008). Role of platelet-derived growth factors in physiology and medicine. Genes Dev, 22, 1276-312.

Grand FH, Clark A, Curtis CE, Reiter A, Minervini MM, Cross NC, ... Stewart J (2007). Two novel imatinib-responsive PDGFRA fusion genes in chronic eosinophilic leukaemia. Br. J. Haematol., 138, 77-81.

Golub TR, Gilliland DG, Barker GF & Lovett M (1994). Fusion of PDGF receptor beta to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. Cell, 77, 307-16.

Edit history

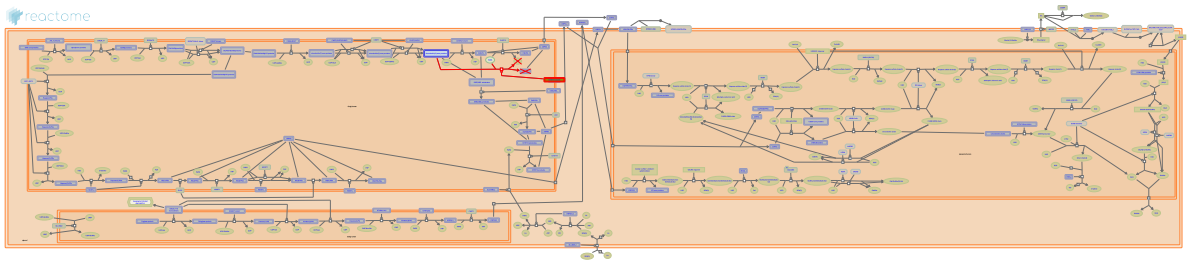
Date	Action	Author
2020-01-08	Created	Rothfels K
2020-02-06	Reviewed	Ip CKM

Date	Action	Author
2020-02-25	Edited	Rothfels K
2020-02-25	Authored	Rothfels K
2020-02-27	Modified	Rothfels K

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

Input	UniProt Id
KDR	P35968

4. Defective CHST3 causes SEDCJD (R-HSA-3595172)



Diseases: spondyloepimetaphyseal dysplasia.

Carbohydrate sulfotransferase 3 (CHST3) transfers sulfate (SO4(2-)) to position 6 of N-acetylgalactosamine (GalNAc) residues of chondroitin-containg proteins resulting in chondroitin sulfate (CS), the predominant glycosaminoglycan present in cartilage. Defects in CHST3 result in spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD; MIM:143095), a bone dysplasia clinically characterized by severe progressive kyphoscoliosis (abnormal curvature of the spine), arthritic changes with joint dislocations and short stature in adulthood (Unger et al. 2010).

References

Chandler K, Nampoothiri S, Bonafe L, Wakeling E, Aytes A, Unger S, ... Velten T (2010). Phenotypic features of carbohydrate sulfotransferase 3 (CHST3) deficiency in 24 patients: congenital dislocations and vertebral changes as principal diagnostic features. Am. J. Med. Genet. A, 152, 2543-9 .

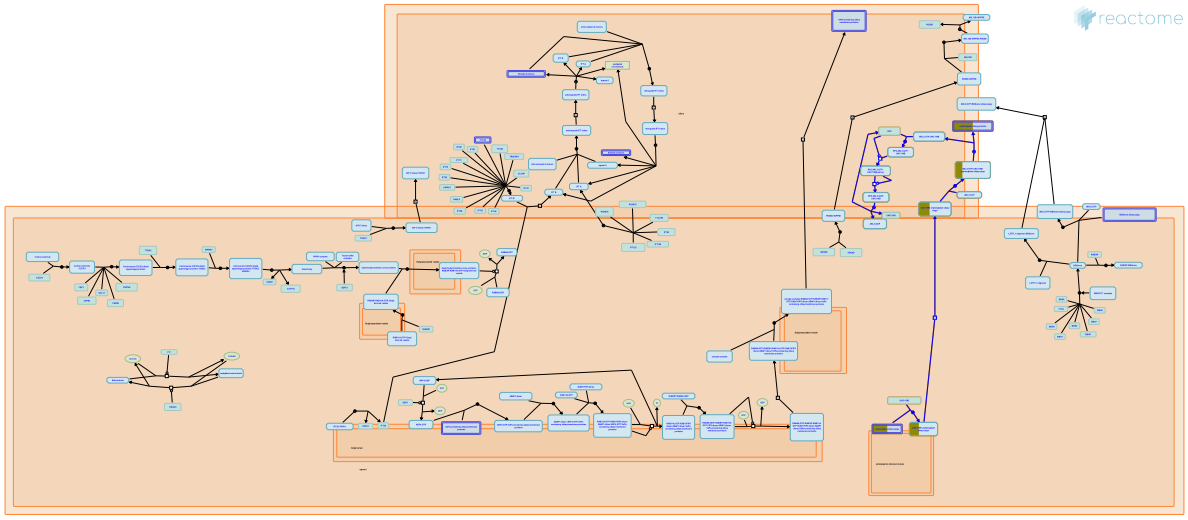
Edit history

Date	Action	Author
2013-05-21	Edited	Jassal B
2013-05-21	Authored	Jassal B
2013-05-21	Created	Jassal B
2014-07-09	Reviewed	Spillmann D
2015-02-09	Modified	Wu G

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

Input	UniProt Id
CHST3	Q7LGC8

5. Trafficking of myristoylated proteins to the cilium (R-HSA-5624138)



A number of myristoylated proteins have been shown to traffic to the cilium in a myristoyl- and UNC119B:ARL3:RP2-dependent fashion. These include the ciliary proteins Nephrocystin 3 (NPHP3) and Cystin 1 (CYS1) (Wright et al, 2011; reviewed in Schwarz et al, 2012). Myristoyl-binding by the ARL3 effector UNC119B is required in an unknown fashion for the transport of the myristoylated cargo to the cilium. At the cilium, a GTPase cycle involving the ARF-like small GTPase ARL3 and its GAP protein RP2 promote the release of the myristoylated proteins into the ciliary membrane and the recycling and ciliary exit of UNC119B (Wright et al, 2011; reviewed in Schwarz et al, 2012). ARL3 plays additional roles in the cilium coordinating the association of IFT A and IFT B complexes with the kinesin motors (Li et al, 2010; reviewed in Li et al, 2012).

References

Ling K, Hu J & Li Y (2012). The emerging role of Arf/Arl small GTPases in cilia and ciliopathies. J. Cell. Biochem., 113, 2201-7.

Sengupta P, Kwong M, Baye LM, Sang L, Sheffield VC, Wright KJ, ... Olivier-Mason A (2011). An ARL3-UNC119-RP2 GTPase cycle targets myristoylated NPHP3 to the primary cilium. Genes Dev. , 25, 2347-60.

Ling K, Wei Q, Hu J, Li Y & Zhang Y (2010). The small GTPases ARL-13 and ARL-3 coordinate intraflagellar transport and ciliogenesis. J. Cell Biol., 189, 1039-51.

Cheetham ME, Schwarz N & Hardcastle AJ (2012). Arl3 and RP2 mediated assembly and traffic of membrane associated cilia proteins. Vision Res., 75, 2-4.

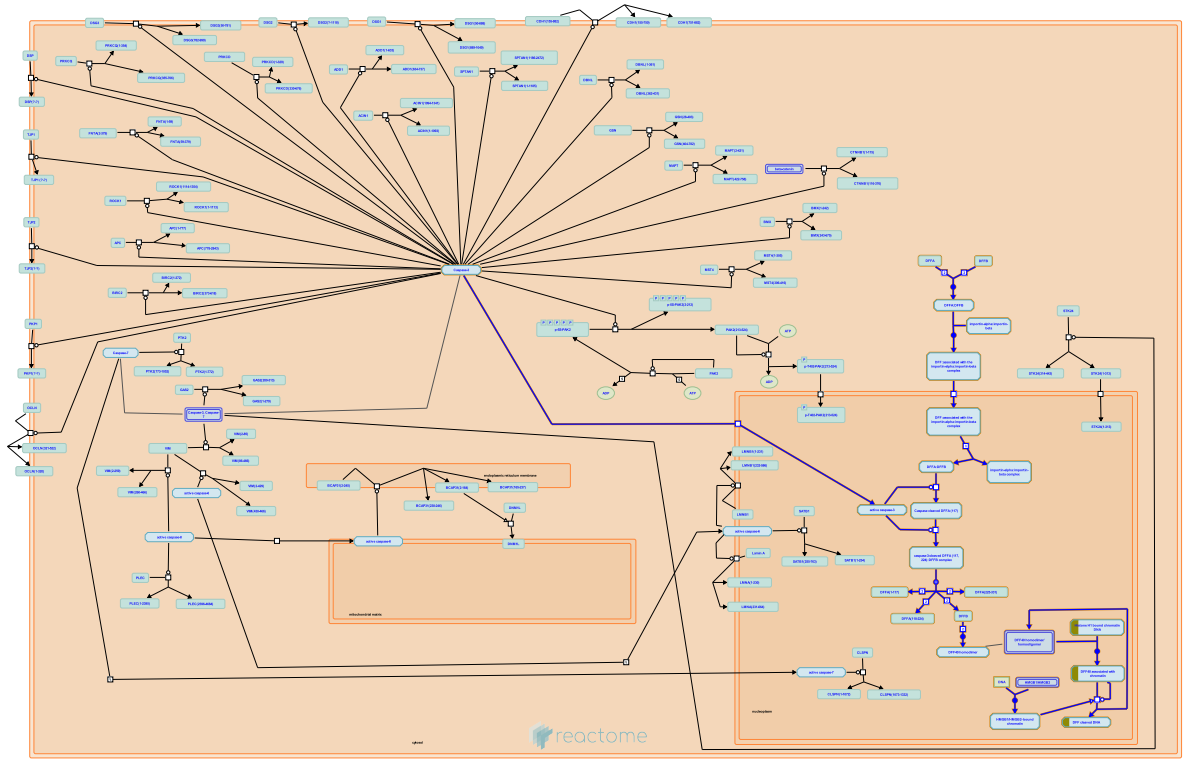
Edit history

Date	Action	Author
2014-09-15	Authored	Rothfels K
2014-09-19	Created	Rothfels K
2014-10-13	Edited	Jassal B
2014-11-10	Reviewed	Lorentzen E
2014-11-14	Reviewed	Goncalves J
2023-03-09	Modified	Wright A

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

Input	UniProt Id
CYS1	Q717R9

6. Apoptosis induced DNA fragmentation (R-HSA-140342)



Cellular compartments: nucleoplasm, cytosol.

DNA fragmentation in response to apoptotic signals is achieved, in part, through the activity of apoptotic nucleases, termed DNA fragmentation factor (DFF) or caspase-activated DNase (CAD) (reviewed in Widlak and Garrard, 2005). In non-apoptotic cells, DFF is a nuclear heterodimer consisting of a 45 kD chaperone and inhibitor subunit (DFF45)/inhibitor of CAD (ICAD-L)] and a 40 kD nuclease subunit (DFF40/CAD)(Liu et al. 1997, 1998; Enari et al. 1998). During apoptosis, activated caspase-3 or -7 cleave DFF45/ICAD releasing active DFF40/CAD nuclease. The activity of DFF is tightly controlled at multiple stages. During translation, DFF45/ICAD, Hsp70, and Hsp40 proteins play a role in insuring the appropriate folding of DFF40 during translation(Sakahira and Nagata, 2002). The nuclease activity of DFF40 is enhanced by the chromosomal proteins histone H1, Topoisomerase II and HMGB1/2(Widlak et al., 2000). In addition, the inhibitors (DFF45/35; ICAD-S/L) are produced in stoichiometric excess (Widlak et al., 2003).

References

Widlak P & Garrard WT (2005). Discovery, regulation, and action of the major apoptotic nucleases DFF40/CAD and endonuclease G. J Cell Biochem, 94, 1078-87.

Li P, Wang X, Widlak P & Garrard WT (2000). Cleavage preferences of the apoptotic endonuclease DFF40 (caspase-activated DNase or nuclease) on naked DNA and chromatin substrates. J Biol Chem, 275, 8226-32.

Garrard W, Liu X, Wang X, Widlak P & Zou H (1999). Activation of the apoptotic endonuclease DFF40 (caspase-activated DNase or nuclease). Oligomerization and direct interaction with histone H1. J Biol Chem, 274, 13836-40.

Cary RB, Lanuszewska J, Widlak P & Garrard WT (2003). Subunit structures and stoichiometries of human DNA fragmentation factor proteins before and after induction of apoptosis. J Biol Chem, 278, 26915-22.

Yokoyama H, Nagata S, Okawa K, Enari M, Iwamatsu A & Sakahira H (1998). A caspase-activated DNase that degrades DNA during apoptosis, and its inhibitor ICAD. Nature, 391, 43-50.

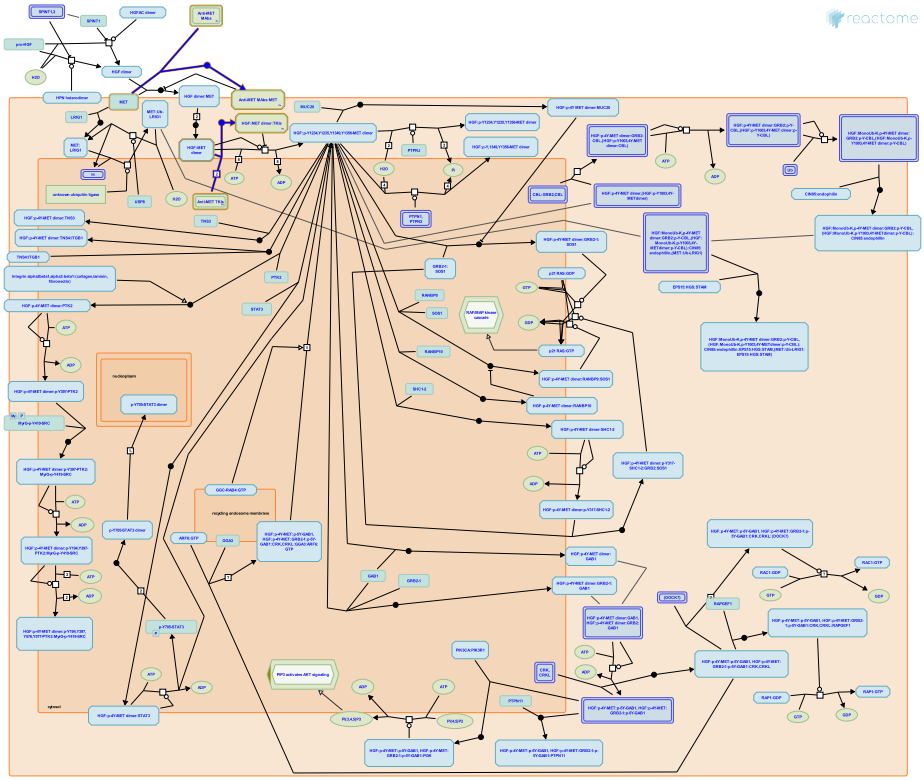
Edit history

Date	Action	Author
2004-02-17	Created	Alnemri E
2008-04-25	Reviewed	Widlak P
2008-04-25	Authored	Matthews L
2008-05-18	Revised	Matthews L
2008-05-18	Edited	Matthews L
2023-03-09	Modified	Wright A

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

Input	UniProt Id
H1-3	P16402

7. Drug-mediated inhibition of MET activation (R-HSA-9734091)



MET receptor tyrosine kinase (RTK) is a proto-oncogene that is frequently aberrantly activated in cancer through gene amplification and/or activating mutations that result in hypersensitivity to HGF stimulation or HGF-independent activation. Oncogenic MET activation can occur as a primary mechanism of malignant transformation or be selected secondarily, as a mechanism of resistance to therapeutics that target related RTKs, such as EGFR. MET targeted anti-cancer therapeutics, either recombinant monoclonal antibodies (MAbs) or small tyrosine kinase inhibitors (TKIs), have shown promise as a first-line agents for the treatment of solid tumors with primary MET activation or as second-line agents for the treatment of solid tumors with acquired MET-mediated resistance to other RTK-targeted therapies (reviewed in Comoglio et al. 2018).

References

Comoglio PM, Boccaccio C & Trusolino L (2018). Known and novel roles of the MET oncogene in cancer: a coherent approach to targeted therapy. Nat Rev Cancer, 18, 341-358.

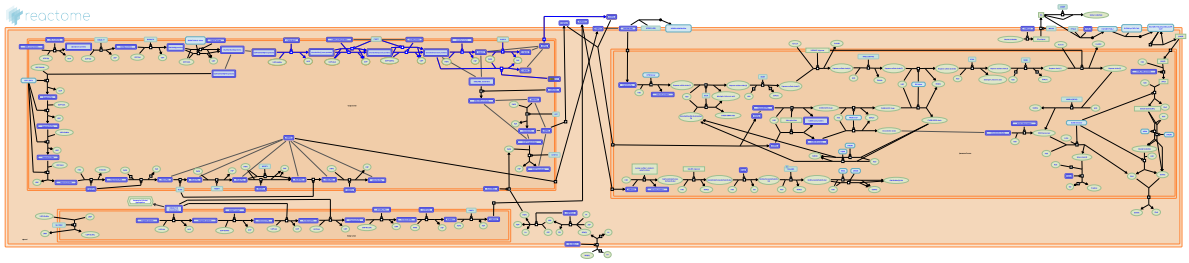
Edit history

Date	Action	Author
2021-06-15	Authored	Orlic-Milacic M
2021-06-15	Created	Orlic-Milacic M
2021-08-05	Reviewed	Kadambat Nair S
2021-08-10	Edited	Orlic-Milacic M
2023-03-09	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35918	P08581			

8. Chondroitin sulfate biosynthesis (R-HSA-2022870)



Chondroitin sulfate (CS) glycosaminoglycan consists of N-acetylgalactosamine (GalNAc) residues alternating in glycosidic linkages with glucuronic acid (GlcA). GalNAc residues are sulfated to varying degrees on 4- and/or 6- positions. The steps below describe the biosynthesis of a simple CS molecule (Pavao et al. 2006, Silbert & Sugumaran 2002).

References

Mourão PA, Pavão MS & Vilela-Silva AC (2006). Biosynthesis of chondroitin sulfate: from the early, precursor discoveries to nowadays, genetics approaches. Adv Pharmacol, 53, 117-40.

Sugumaran G & Silbert JE (2002). Biosynthesis of chondroitin/dermatan sulfate. IUBMB Life, 54, 177-86.

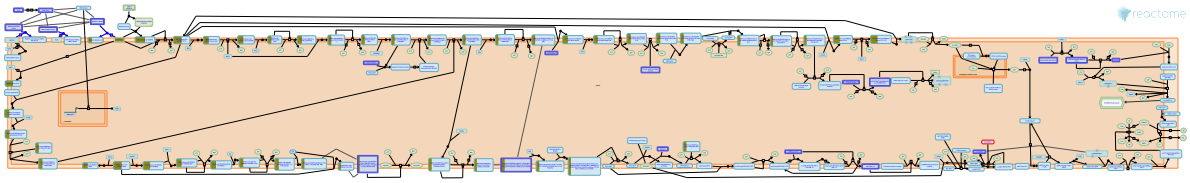
Edit history

Date	Action	Author
2011-12-01	Edited	Jassal B
2011-12-01	Authored	Jassal B
2011-12-01	Created	Jassal B
2012-03-28	Reviewed	D'Eustachio P
2023-03-09	Modified	Wright A

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

Input	UniProt Id
CHST3	Q7LGC8

9. VEGF binds to VEGFR leading to receptor dimerization (R-HSA-195399)



Cellular compartments: plasma membrane.

The binding of VEGF ligands to VEGFR receptors in the cell membrane induces dimerization and activation of the latter, initiating intracellular signaling cascades that result in proliferation, survival, migration and increased permeability of vascular endothelial cells (Matsumoto and Mugishima, 2006). The receptors predominantly form homodimers but heterodimers between VEGFR-1 and -2 have been observed. Although both VEGFR-1 and -2 are expressed in the vascular endothelium, the angiogenic activities of VEGFs are transduced mainly through VEGFR-2 in vivo.

References

Dimberg A, Kreuger J, Olsson AK & Claesson-Welsh L (2006). VEGF receptor signalling - in control of vascular function. Nat Rev Mol Cell Biol, 7, 359-71.

Matsumoto T & Mugishima H (2006). Signal transduction via vascular endothelial growth factor (VEGF) receptors and their roles in atherogenesis. J Atheroscler Thromb, 13, 130-5.

Matsumoto T, Cross MJ, Dixelius J & Claesson-Welsh L (2003). VEGF-receptor signal transduction. Trends Biochem Sci, 28, 488-94.

Edit history

Date	Action	Author
2007-04-06	Created	Gopinathrao G
2008-02-28	Reviewed	Claesson-Welsh L
2013-08-30	Edited	Garapati P V
2013-08-30	Authored	Garapati P V
2023-03-09	Modified	Wright A

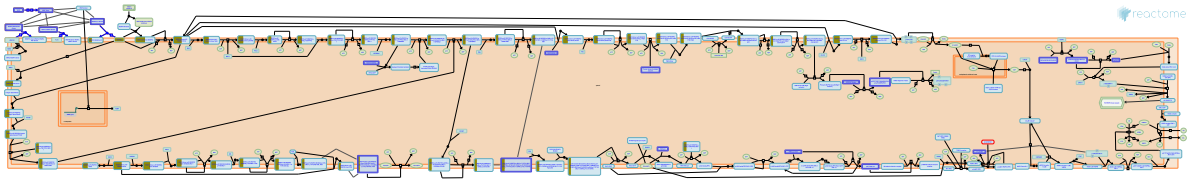
1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
KDR	P35968

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35968	P35968, P35916			

10. VEGF ligand-receptor interactions (R-HSA-194313)



Cellular compartments: plasma membrane.

The VEGF family is encoded by seven genes (VEGF-A, B, C, D, E: PLGF (Placenta Growth Factor)-1, 2). Six isoforms of VEGF-A protein, containing 121, 145, 165, 183, 189, and 206 amino acid residues, and two isoforms of VEGF-B (167 and 186 residues) are specified by alternatively spliced mRNAs. The active form of each of these proteins is a homodimer.

The specificities of the three VEGF tyrosine kinase receptors, VEGFR-1, VEGFR-2 and VEGFR-3, for these ligands are shown in the figure (Hicklin and Ellis 2005). All VEGF-A isoforms bind both VEGFR-1 and VEGFR-2; PLGF-1 and -2, and VEGF-B isoforms bind only VEGFR-1; VEGF-E binds VEGFR-2; and VEGF-C and -D bind both VEGFR-2 and -3. VEGF-D undergoes a complex series of post-translational modifications that results in secreted forms with increased activity toward VEGFR-3 and VEGFR-2.

Two co-receptor proteins in the cell membrane, neuropilin (NRP)-1 and NRP-2, interact with VEGFR proteins to increase the affinity of the latter for their ligands (Neufeld et al.,2002). They differ from VEGFR proteins in not having intracellular signaling domains.

References

Shibuya M & Claesson-Welsh L (2006). Signal transduction by VEGF receptors in regulation of angiogenesis and lymphangiogenesis. Exp Cell Res, 312, 549-60.

Dimberg A, Kreuger J, Olsson AK & Claesson-Welsh L (2006). VEGF receptor signalling - in control of vascular function. Nat Rev Mol Cell Biol, 7, 359-71.

Matsumoto T & Mugishima H (2006). Signal transduction via vascular endothelial growth factor (VEGF) receptors and their roles in atherogenesis. J Atheroscler Thromb, 13, 130-5.

Matsumoto T, Cross MJ, Dixelius J & Claesson-Welsh L (2003). VEGF-receptor signal transduction. Trends Biochem Sci, 28, 488-94.

Edit history

Date	Action	Author
2007-03-12	Created	Gopinathrao G
2008-02-28	Reviewed	Claesson-Welsh L
2013-08-30	Edited	Garapati P V
2013-08-30	Authored	Garapati P V
2023-03-09	Modified	Wright A

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

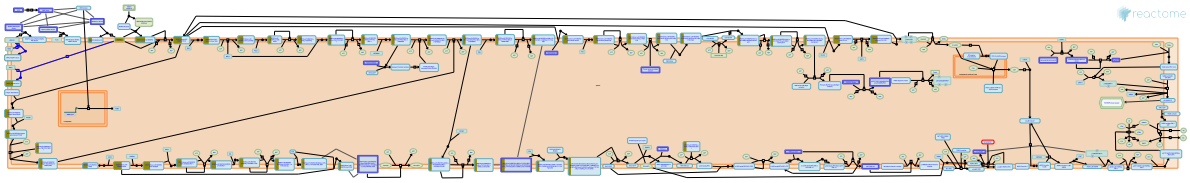
Input	UniProt Id
KDR	P35968

Input	UniProt Id

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35968	P35968, P35916			

11. Neurophilin interactions with VEGF and VEGFR (R-HSA-194306)



Cellular compartments: plasma membrane.

The plasma membrane-associated Neuropilin receptors NRP-1 and -2 bind some of the VEGF proteins and associate with VEGF receptor proteins. NRP-1 binds VEGF-A165, -B, and PLGF-2; NRP-2 also binds VEGF-A165 and PLGF-2, as well as VEGF-A145 and -C. The Neurolipin receptors appear to act as cofactors for the VEGF receptors, increasing their affinities for specific VEGF ligands, although the importance of this function in vivo remains unclear (Neufeld et al. 2002).

References

Herzog Y, Kessler O & Neufeld G (2002). The interaction of Neuropilin-1 and Neuropilin-2 with tyrosine-kinase receptors for VEGF. Adv Exp Med Biol, 515, 81-90.

Edit history

Date	Action	Author
2007-03-12	Created	Gopinathrao G
2008-02-28	Reviewed	Claesson-Welsh L
2013-08-30	Edited	Garapati P V
2013-08-30	Authored	Garapati P V
2023-03-09	Modified	Wright A

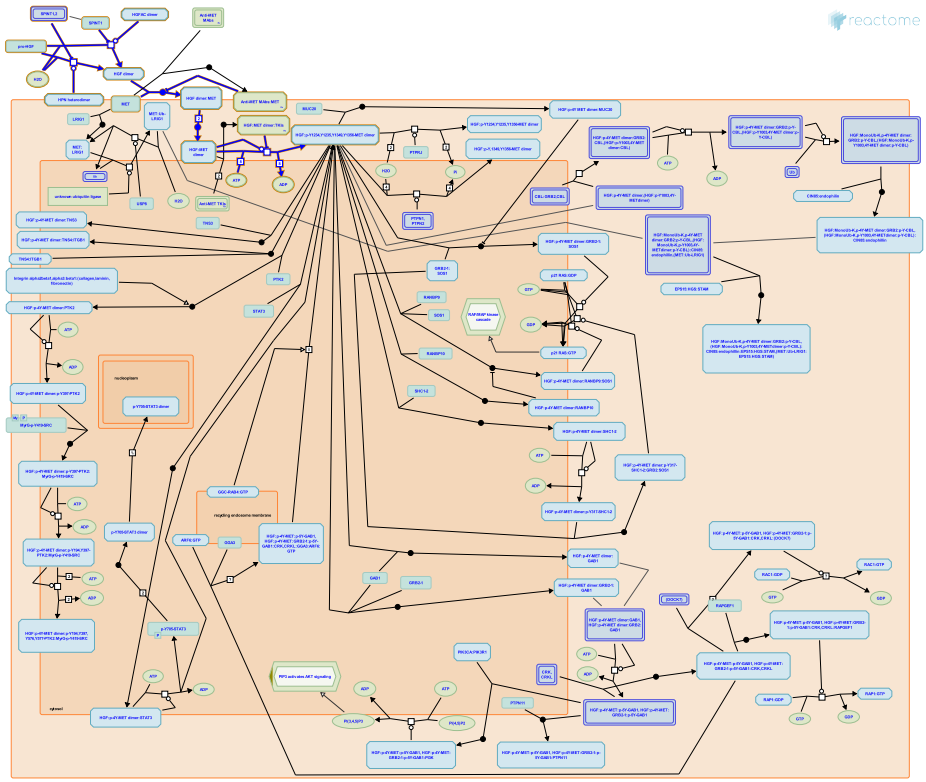
1 submitted entities found in this pathway, mapping to 1 Reactome entities

Input	UniProt Id
KDR	P35968

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35968	P35968, O14786			

12. MET Receptor Activation (R-HSA-6806942)



Hepatocyte growth factor (HGF), the ligand for MET receptor tyrosine kinase (RTK), is secreted into the extracellular matrix (ECM) as an inactive single chain precursor (pro-HGF). The biologically active HGF is the heterodimer of alpha and beta chains that are produced via proteolytic cleavage of pro-HGF by the plasma membrane bound serine protease Hepsin (HPN) (Kirchhofer et al. 2005, Owen et al. 2010) or the ECM-associated serine protease Hepatocyte growth factor activator (HGFAC, commonly known as HGFA) (Shia et al. 2005). HGF binds to the extracellular SEMA and PSI domains of MET RTK, inducing a conformational change that enables MET dimerization or oligomerization (Kirchhofer et al. 2004, Stamos et al. 2004, Hays and Watowich 2004, Gherardi et al. 2006). MET dimers trans-autophosphorylate on tyrosine residues in the activation loop, leading to increased kinase activity, and on tyrosine residues at the cytoplasmic tail that serve as docking sites for adapter proteins involved in MET signal transduction (Ferracini et al. 1991, Longati et al. 1994, Rodrigues and Park 1994, Ponzetto et al. 1994).

CD44v6 was implicated as a MET co-receptor, but its role has been disputed (Orian-Rousseau et al. 2002, Dortet et al. 2010, Olaku et al. 2011, Hasenauer et al. 2013, Elliot et al. 2014).

References

Kirchhofer D, Shia S, Corpuz RT, Stamos J, Santell L, Fan B, ... Lazarus RA (2005). Conformational lability in serine protease active sites: structures of hepatocyte growth factor activator (HGFA) alone and with the inhibitory domain from HGFA inhibitor-1B. J. Mol. Biol., 346, 1335-49.

Kirchhofer D, Lipari MT, Fan B, Peek M, Billeci K & Moran P (2005). Hepsin activates pro-hepatocyte growth factor and is inhibited by hepatocyte growth factor activator inhibitor-1B (HAI-1B) and HAI-2. FEBS Lett., 579, 1945-50.

Ofverstedt LG, Sandin S, Svergun DI, Finch J, Miguel RN, Petoukhov MV, ... Blundell TL (2006). Structural basis of hepatocyte growth factor/scatter factor and MET signalling. Proc. Natl. Acad. Sci. U.S.A., 103, 4046-51.

Elliott VA, Zaytseva YY, Evers BM & Rychahou P (2014). Activation of c-Met and upregulation of CD44 expression are associated with the metastatic phenotype in the colorectal cancer liver metastasis model. PLoS ONE, 9, e97432.

Malinger D, Orian-Rousseau V, Hasenauer S, Pace G, von Au A, Koschut D & Matzke A (2013). Internalization of Met requires the co-receptor CD44v6 and its link to ERM proteins. PLoS ONE, 8, e62357.

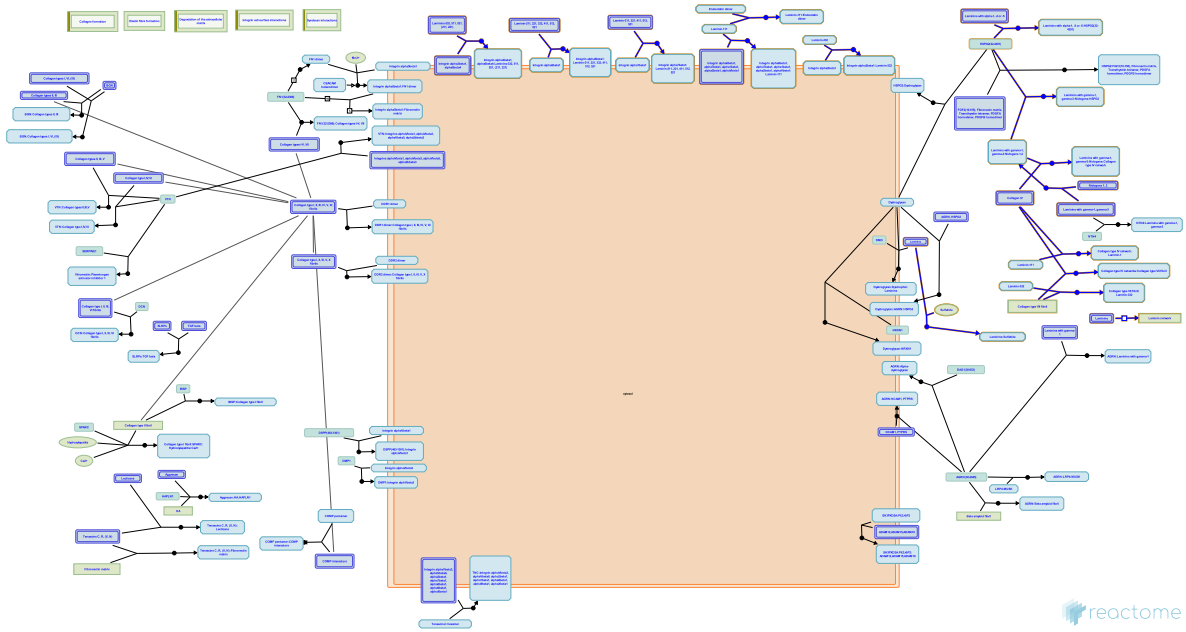
Edit history

Date	Action	Author
2015-10-28	Created	Orlic-Milacic M
2016-06-14	Edited	Orlic-Milacic M
2016-06-14	Authored	Orlic-Milacic M
2016-07-11	Reviewed	Heynen G, Birchmeier W
2023-03-09	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35918	P08581			

13. Laminin interactions (R-HSA-3000157)



Laminins are a large family of conserved, multidomain trimeric basement membrane proteins. There are many theoretical trimer combinations but only 18 have been described (Domogatskaya et al. 2012, Miner 2008, Macdonald et al. 2010) and the existence of isoforms laminin-212 and/or laminin-222 (Durbeej et al. 2010) awaits further confirmation. The chains assemble through coiled-coil domains at their C-terminal end. Alpha chains additionally have a large C-terminal globular domain containing five LG subdomains (LG1-5). The N termini are often referred to as the short arms. These have varying numbers of laminin-type epidermal growth factor-like (LE) repeats. Trimer assembly is controlled by highly specific coiled-coil interactions (Domogatskaya et al. 2012). Some laminin isoforms are modified extracellularly by proteolytic processing at the N- or C-terminal ends prior to their binding to cellular receptors or other matrix molecules (Tzu & Marinkovitch 2008).

The cell adhesion properties of laminins are mediated primarily through the alpha chain G domain to integrins, dystroglycan, Lutheran glycoprotein, or sulfated glycolipids. The N-terminal globular domains of the alpha-1 (Colognato-Pyke et al. 1995) and alpha-2 chains (Colognato et al. 1997) and globular domains VI (Nielsen & Yamada 2001) and IVa (Sasaki & Timpl 2001) of the alpha-5 chain can bind to several integrin isoforms (alpha1beta1, alpha2beta1, alpha3beta1, and alphaVbeta3), which enables cell binding at both ends of laminins with these alpha chains.

References

Domogatskaya A, Rodin S & Tryggvason K (2012). Functional diversity of laminins. Annu. Rev. Cell Dev. Biol., 28, 523-53.

Edit history

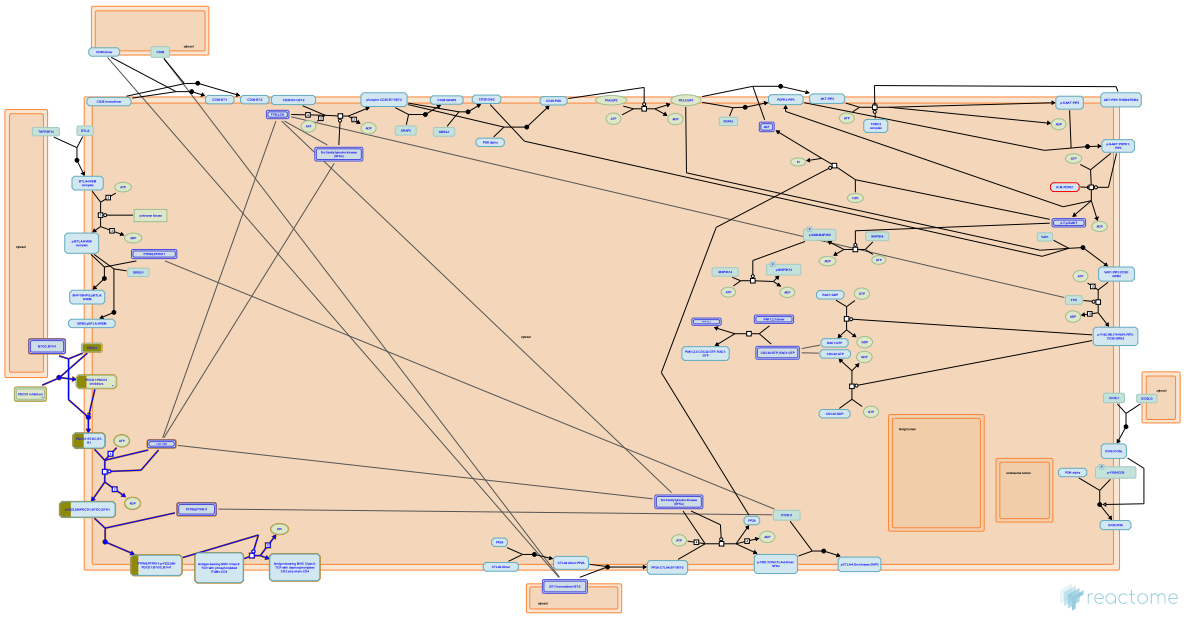
Date	Action	Author
2008-05-07	Reviewed	Hynes R, Humphries MJ, Yamada KM
2012-08-08	Authored	Jupe S
2013-01-24	Created	Jupe S
2013-08-13	Edited	Jupe S

Date	Action	Author
2013-08-13	Reviewed	Ricard-Blum S
2023-03-09	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35968	P98160			

14. PD-1 signaling (R-HSA-389948)



Cellular compartments: plasma membrane.

The Programmed cell death protein 1 (PD-1) is one of the negative regulators of TCR signaling. PD-1 may exert its effects on cell differentiation and survival directly by inhibiting early activation events that are positively regulated by CD28 or indirectly through IL-2. PD-1 ligation inhibits the induction of the cell survival factor Bcl-xL and the expression of transcription factors associated with effector cell function, including GATA-3, Tbet, and Eomes. PD-1 exerts its inhibitory effects by bringing phosphatases SHP-1 and SHP-2 into the immune synapse, leading to dephosphorylation of CD3-zeta chain, PI3K and AKT.

References

Fife BT & Bluestone JA (2008). Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev, 224, 166-82.

Keir ME, Sharpe AH, Freeman GJ & Butte MJ (2008). PD-1 and its ligands in tolerance and immunity . Annu Rev Immunol, 26, 677-704.

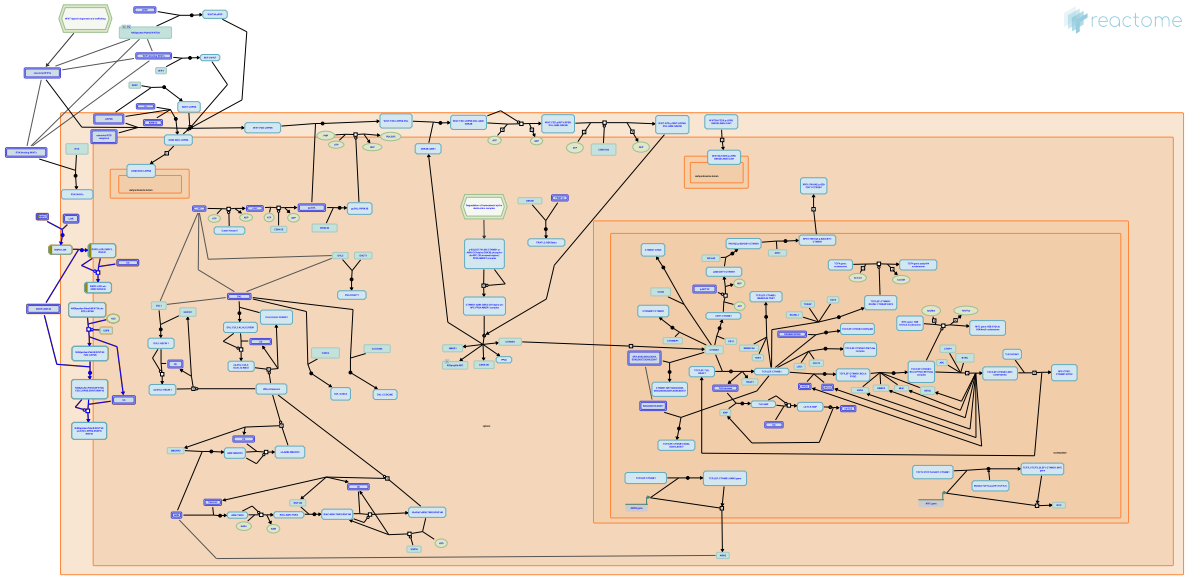
Edit history

Date	Action	Author
2008-12-16	Edited	Garapati P V
2008-12-16	Authored	Garapati P V
2009-01-21	Created	Garapati P V
2009-06-01	Reviewed	Bluestone JA, Esensten J
2023-03-09	Modified	Wright A

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

Input	UniProt Id
PDCD1	Q15116

15. Regulation of FZD by ubiquitination (R-HSA-4641263)



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

References

Gagliardi M, Vincent JP & Piddini E (2008). Endocytosis: a positive or a negative influence on Wnt signalling?. Traffic, 9, 1-9.

Mickanin C, Zhang Y, Bouwmeester T, Zamponi R, Xie Y, Liu D, ... Mao X (2012). ZNRF3 promotes Wnt receptor turnover in an R-spondin-sensitive manner. Nature, 485, 195-200.

Watanabe W, Goto S, Komada M, Awano W, Yamamoto-Hino M & Mukai A (2010). Balanced ubiquitylation and deubiquitylation of Frizzled regulate cellular responsiveness to Wg/Wnt. EMBO J., 29, 2114-25.

Spence JR & Fearon ER (2012). Cancer biology: a new RING to Wnt signaling. Curr. Biol., 22, R849-51.

Abo A & Clevers HC (2012). Modulating WNT receptor turnover for tissue repair. Nat. Biotechnol., 30, 835-6.

Edit history

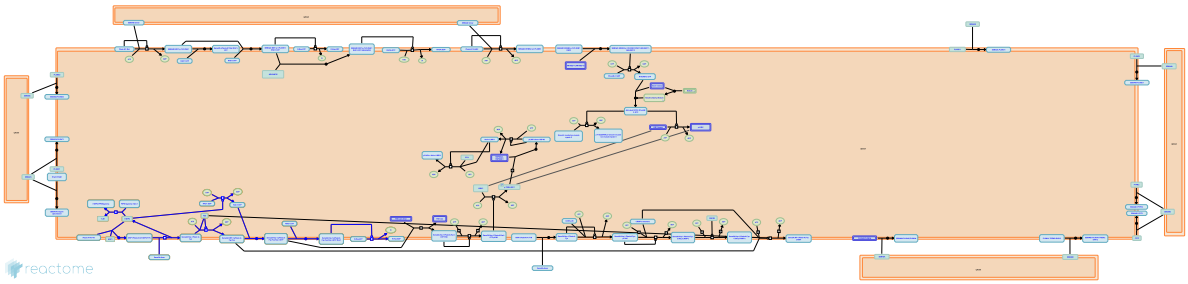
Date	Action	Author
2007-09-04	Edited	Matthews L

Date	Action	Author
2013-09-23	Authored	Rothfels K
2013-09-28	Created	Rothfels K
2013-10-03	Edited	Gillespie ME
2014-01-22	Reviewed	Rajakulendran N
2014-02-15	Reviewed	van Amerongen R
2014-04-22	Reviewed	Kikuchi A
2023-03-09	Modified	Wright A

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

Input	UniProt Id
RSPO1	Q2MKA7

16. SEMA3A-Plexin repulsion signaling by inhibiting Integrin adhesion (R-HSA-399955)



Sema3A, a prototypical semaphorin, acts as a chemorepellent or a chemoattractant for axons by activating a receptor complex comprising neuropilin-1 as the ligand-binding subunit and plexin-A1 as the signal-transducing subunit. Sema3A inhibits cell migration by inhibiting integrin ligand-binding activity.

References

Zhang H, Yoshida J, Toyofuku T, Kumanogoh A, Sugimoto T, Kikutani H & Hori M (2005). FARP2 triggers signals for Sema3A-mediated axonal repulsion. Nat Neurosci, 8, 1712-9.

Kessler O & Neufeld G (2008). The semaphorins: versatile regulators of tumour progression and tumour angiogenesis. Nat Rev Cancer, 8, 632-45.

Zhou Y, Pasterkamp RJ & Gunput RA (2008). Semaphorin signaling: progress made and promises ahead. Trends Biochem Sci, 33, 161-70.

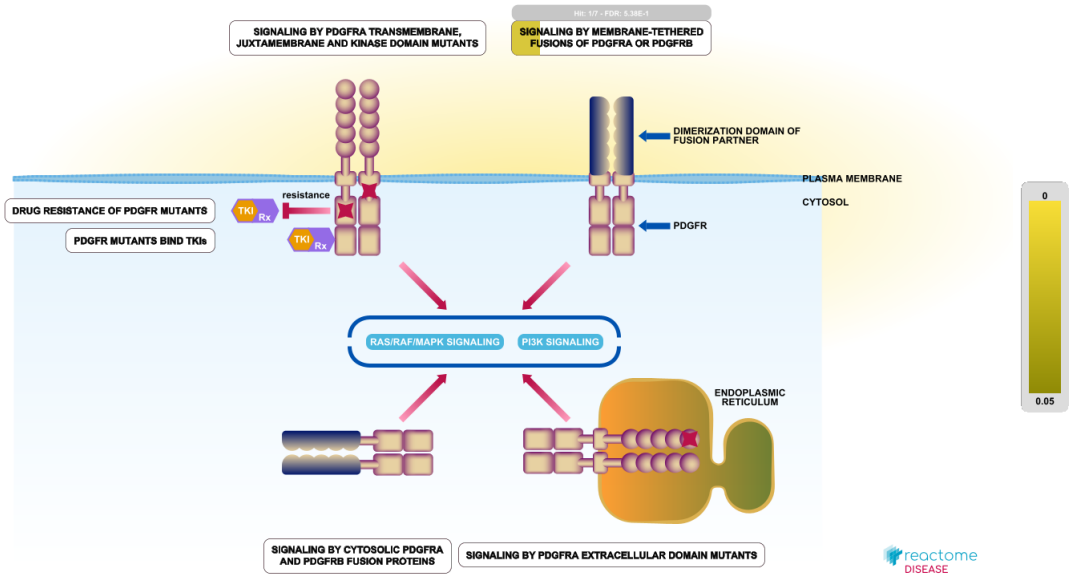
Edit history

Date	Action	Author
2009-03-23	Edited	Garapati P V
2009-03-23	Authored	Garapati P V
2009-03-23	Created	Garapati P V
2009-09-02	Reviewed	Kumanogoh A, Kikutani H
2023-03-09	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35968	O14786			

17. Signaling by PDGFR in disease (R-HSA-9671555)



Diseases: cancer.

PDGFRA and PDGFRB are type III receptor tyrosine kinases that promote development and maintenance of mesenchymal tissues, including vascular smooth muscle, kidney, intestine, skin and lung, among others (reviewed in Tallquist and Kazlauskas, 2004; reviewed in Wang et al, 2016). Signaling through PDGF receptors stimulates cell proliferation and survival through activation of downstream signaling pathways including the RAS-MAP kinase cascade, PI3K signaling and STAT signaling (reviewed in Roskoski, 2018). Aberrant signaling through PDGF receptors is implicated in a number of human diseases. Point mutations in PDGFRA and, to a lesser extent, PDGFRB are implicated in a number of cancers, such as gastrointestinal stromal tumors (GIST; 5-10% mutation frequency in PDGFRA) and haematological cancers (Corless et al, 2005; Wang et al, 2016; reviewed in Klug et al, 2018). In addition, amplified signaling through the PDGF pathway can arise through gene fusion events or overexpression of ligand or receptor through gene amplification (Ozawa et al, 2010; Verhaak et al, 2010; reviewed in Appiah-Kubi et al, 2017).

References

Yao X, Chen Y, Wu M, Qian H, Wang Y, Wu Y & Appiah-Kubi K (2016). The platelet-derived growth factors (PDGFs) and their receptors (PDGFRs) are major players in oncogenesis, drug resistance, and attractive oncologic targets in cancer. Growth Factors, 34, 64-71.

Ding L, Qi Y, Perou CM, Tamayo P, Wang V, Mesirov JP, ... O'Kelly M (2010). Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell, 17, 98-110.

Roskoski R (2018). The role of small molecule platelet-derived growth factor receptor (PDGFR) inhibitors in the treatment of neoplastic disorders. Pharmacol. Res., 129, 65-83.

Yao X, Chen Y, Wu M, Qian H, Wang Y, Wu Y, ... Lan T (2017). Platelet-derived growth factor receptors (PDGFRs) fusion genes involvement in hematological malignancies. Crit. Rev. Oncol. Hematol., 109, 20-34.

Kazlauskas A & Tallquist M (2004). PDGF signaling in cells and mice. Cytokine Growth Factor Rev., 15, 205-13.

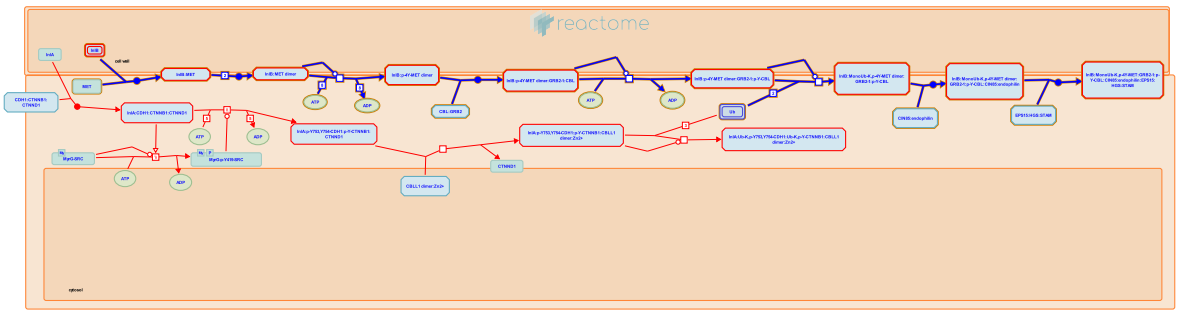
Edit history

Date	Action	Author
2019-12-19	Created	Rothfels K
2020-02-06	Reviewed	Ip CKM
2020-02-25	Edited	Rothfels K
2020-02-25	Authored	Rothfels K
2020-11-11	Modified	Matthews L

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

Input	UniProt Id
KDR	P35968

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



Diseases: listeriosis.

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

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

References

Heinz DW, Gherardi E, Ferraris DM, Niemann HH & Di Y (2010). Ligand-mediated dimerization of the Met receptor tyrosine kinase by the bacterial invasion protein InlB. J. Mol. Biol., 395, 522-32.

Veiga E & Cossart P (2005). Listeria hijacks the clathrin-dependent endocytic machinery to invade mammalian cells. Nat. Cell Biol., 7, 894-900.

Park M, Naujokas M, Ireton K & Shen Y (2000). InIB-dependent internalization of Listeria is mediated by the Met receptor tyrosine kinase. Cell, 103, 501-10.

Heinz DW, Ferraris D, Schmidt S, Gherardi E, van den Heuvel J, Jäger V, ... Niemann HH (2007). Structure of the human receptor tyrosine kinase met in complex with the Listeria invasion protein InlB. Cell, 130, 235-46.

Orian-Rousseau V, Tenenbaum T, Schwerk C, Matzke A, Niemann HH & Jung C (2009). Involvement of CD44v6 in InlB-dependent Listeria invasion. Mol. Microbiol., 72, 1196-207.

Edit history

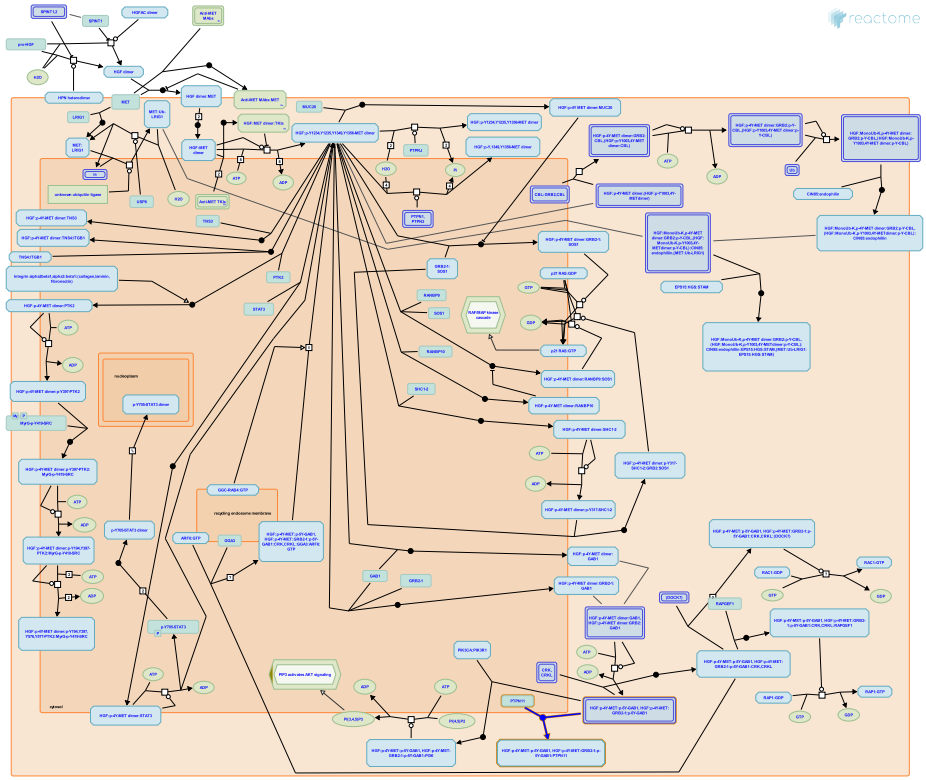
Date	Action	Author
2016-06-03	Created	Orlic-Milacic M

Date	Action	Author
2016-06-14	Authored	Orlic-Milacic M
2016-10-25	Reviewed	Schwerk C
2016-10-26	Edited	Orlic-Milacic M
2023-03-15	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35918	P08581			

19. MET activates PTPN11 (R-HSA-8865999)



PTPN11 (SHP2), recruited to activated MET receptor through GAB1, is phosphorylated in response to HGF treatment, although phosphorylation sites and direct MET involvement have not been examined (Schaeper et al. 2000, Duan et al. 2006). Phosphorylation of PTPN11 in response to HGF treatment is required for the recruitment and activation of sphingosine kinase SPHK1, which may play a role in HGF-induced cell scattering (Duan et al. 2006). While PTPN11 promotes MAPK3/1 (ERK1/2) signaling downstream of MET, it can also dephosphorylate MET on unidentified tyrosine residues (Furcht et al. 2014).

References

Kempkes B, Fuchs KP, Birchmeier W, Sachs M, Gehring NH & Schaeper U (2000). Coupling of Gab1 to c-Met, Grb2, and Shp2 mediates biological responses. J. Cell Biol., 149, 1419-32.

Yu WM, Zhang QW, Wang LS, Wang H, Wu CT, Duan HF & Qu CK (2006). Shp-2 tyrosine phosphatase is required for hepatocyte growth factor-induced activation of sphingosine kinase and migration in embryonic fibroblasts. Cell. Signal., 18, 2049-55.

Lazzara MJ, Furcht CM, Mathew LK, Simon MC, Muñoz Rojas AR, Skuli N & Buonato JM (2014). Multivariate signaling regulation by SHP2 differentially controls proliferation and therapeutic response in glioma cells. J. Cell. Sci., 127, 3555-67.

Edit history

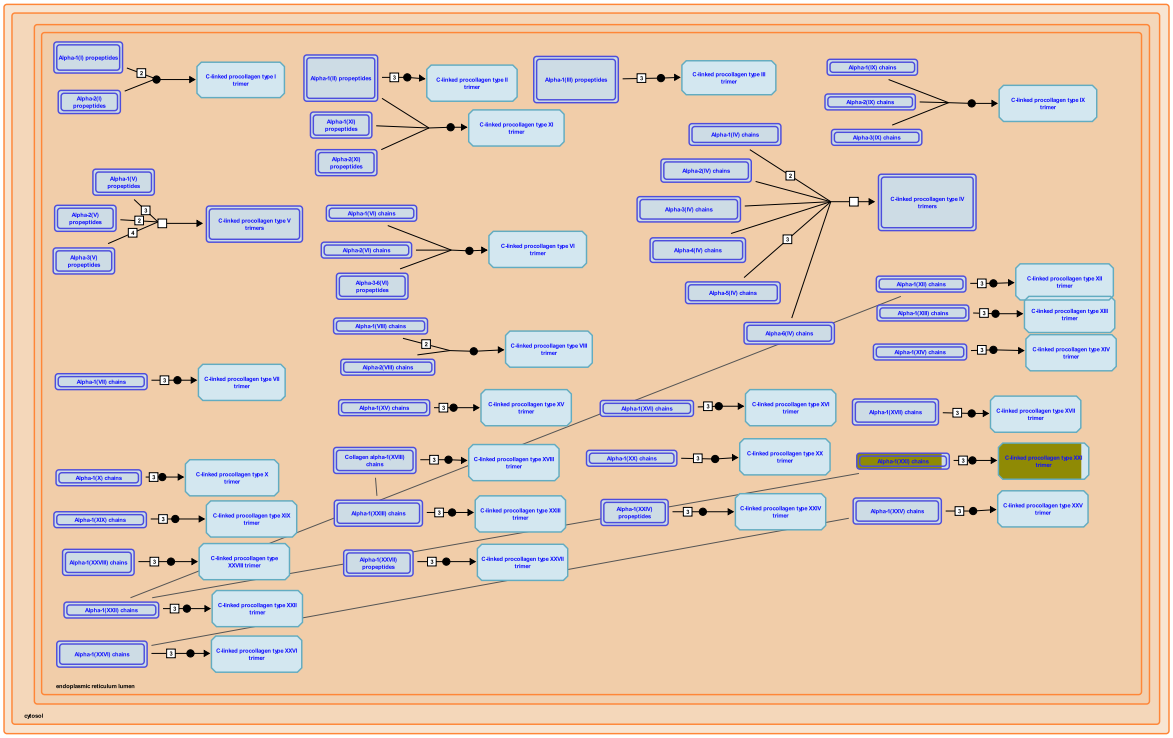
Date	Action	Author
2016-03-29	Created	Orlic-Milacic M
2016-06-14	Edited	Orlic-Milacic M
2016-06-14	Authored	Orlic-Milacic M

Date	Action	Author
2016-07-11	Reviewed	Heynen G, Birchmeier W
2023-03-15	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
PDCD1	Q15116	Q06124			

20. Collagen chain trimerization (R-HSA-8948216)



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The C-propeptides of collagen propeptide chains are essential for the association of three peptide chains into a trimeric but non-helical procollagen. This initial binding event determines the composition of the trimer, brings the individual chains into the correct register and initiates formation of the triple helix at the C-terminus, which then proceeds towards the N-terminus in a zipper-like fashion (Engel & Prockop 1991). Most early refolding studies were performed with collagen type III, which contains a disulfide linkage at the C-terminus of its triple helix (Bächinger et al. 1978, Bruckner et al. 1978) that acts as a permanent linker even after removal of the non-collagenous domains.

Mutations within the C-propeptides further suggest that they are crucial for the correct interaction of the three polypeptide chains and for subsequent correct folding (refs. in Boudko et al. 2011).

References

Timpl R, Brückner P, Engel J & Bächinger HP (1978). The role of cis-trans isomerization of peptide bonds in the coil leads to and comes from triple helix conversion of collagen. Eur J Biochem, 90, 605-13.

Byers PH, Bornstein P, Click EM & Harper E (1975). Interchain disulfide bonds in procollagen are located in a large nontriple-helical COOH-terminal domain. Proc Natl Acad Sci U S A, 72, 3009-13 .

Edit history

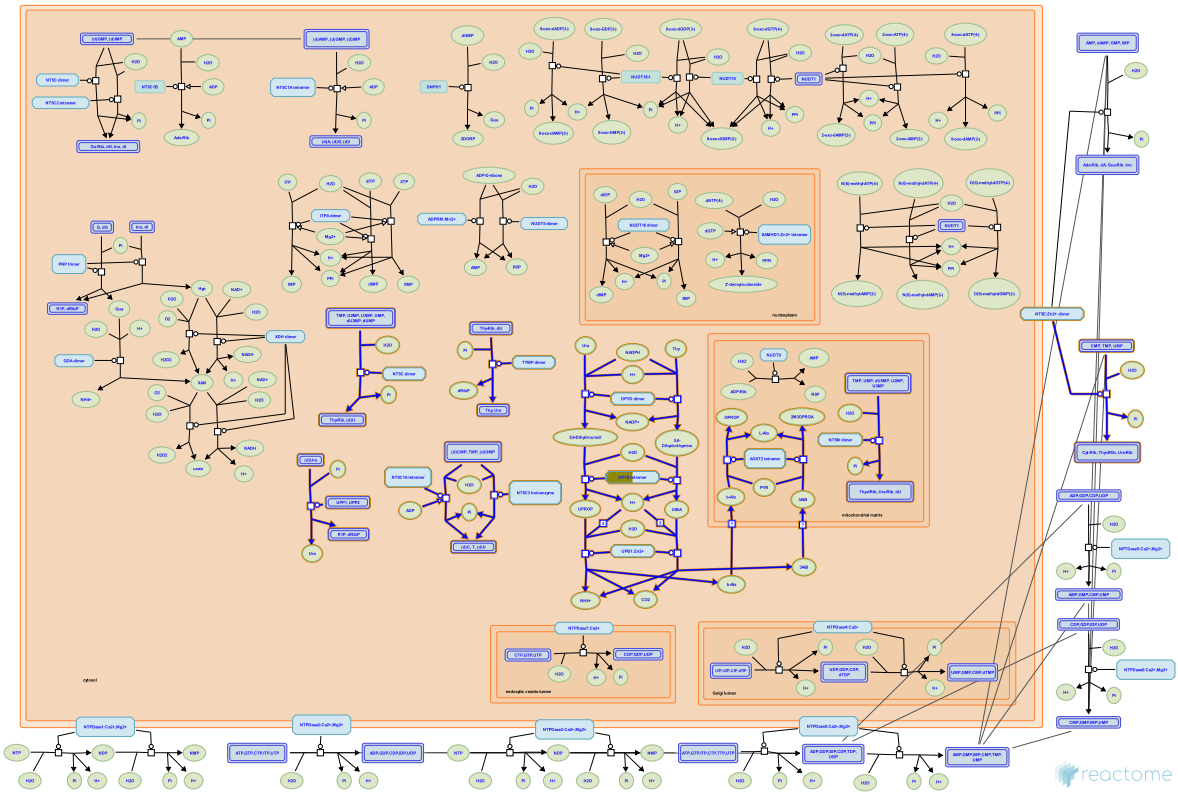
Date	Action	Author
2012-04-11	Authored	Jupe S
2012-05-24	Reviewed	Canty-Laird EG
2016-11-03	Edited	Jupe S

Date	Action	Author
2016-11-11	Created	Jupe S
2023-03-09	Modified	Wright A

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

Input	UniProt Id
COL21A1	Q96P44

21. Pyrimidine catabolism (R-HSA-73621)



In parallel sequences of three reactions each, thymine is converted to beta-aminoisobutyrate and uracil is converted to beta-alanine. Both of these molecules are excreted in human urine and appear to be normal end products of pyrimidine catabolism (Griffith 1986; Webster et al. 2001). Mitochondrial AGXT2, however, can also catalyze the transamination of both molecules with pyruvate, yielding 2-oxoacids that can be metabolized further by reactions of branched-chain amino acid and short-chain fatty acid catabolism (Tamaki et al. 2000). The importance of these reactions in normal human pyrimidine catabolism has not been well worked out.

References

Matsuda K, Sakata SF & Tamaki N (2000). Purification, properties, and sequencing of aminoisobutyrate aminotransferases from rat liver. Methods Enzymol, 324, 376-89.

Griffith OW (1986). Beta-amino acids: mammalian metabolism and utility as alpha-amino acid analogues. Annu Rev Biochem, 55, 855-878.

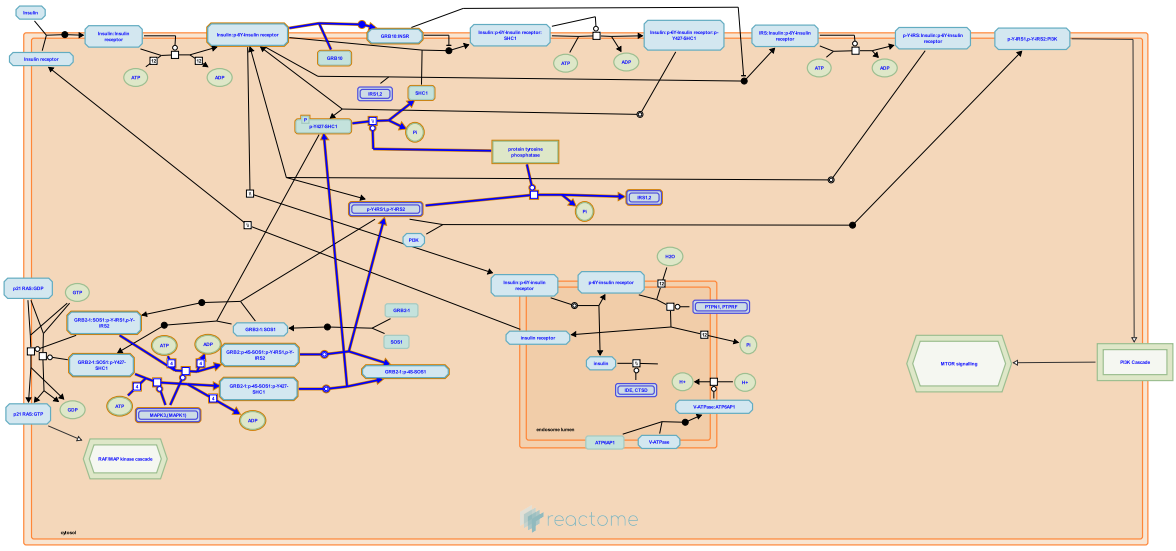
Edit history

Date	Action	Author
2003-06-17	Authored	Jassal B
2003-06-17	Created	Jassal B
2010-02-06	Revised	D'Eustachio P
2023-03-09	Modified	Wright A

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

Input	UniProt Id
DPYS	Q14117

22. Signal attenuation (R-HSA-74749)



Cellular compartments: cytosol.

Now with the complete receptor-ligand dissociation and subsequent degradation of insulin in the endosomal lumen, the endosomally associated protein tyrosine phosphatases (PTPs) complete the receptor dephosphorylation. So too are all the receptor substrates dephosphorylated leading to the collapse of the signalling complexes and signal attenuation.

References

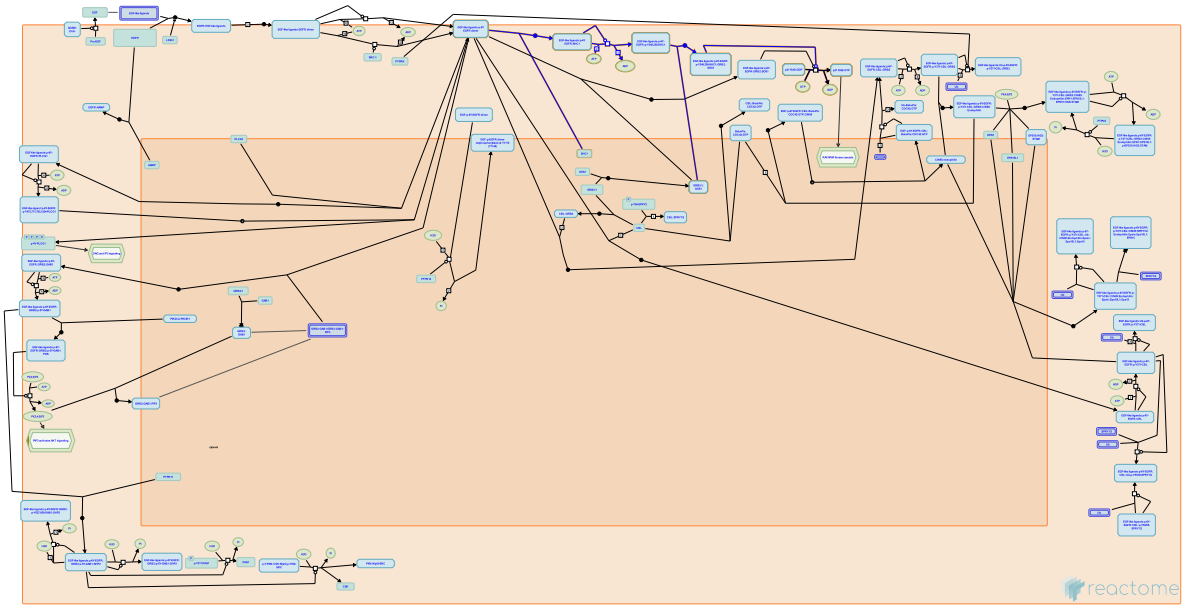
Edit history

Date	Action	Author
2003-07-28	Authored	
2003-07-31	Created	Bevan AP
2023-03-15	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35968	P29353			

23. SHC1 events in EGFR signaling (R-HSA-180336)



GRB2 can bind EGFR directly or through another SH2-containing protein, SHC1. This association leads to RAS activation.

References

Pelicci G, Bonfini L, Migliaccio E, Lanfrancone L & Pelicci PG (1996). Not all Shc's roads lead to Ras. Trends Biochem Sci, 21, 257-61.

Sorkin A (2001). Internalization of the epidermal growth factor receptor: role in signalling. Biochem Soc Trans, 29, 480-4.

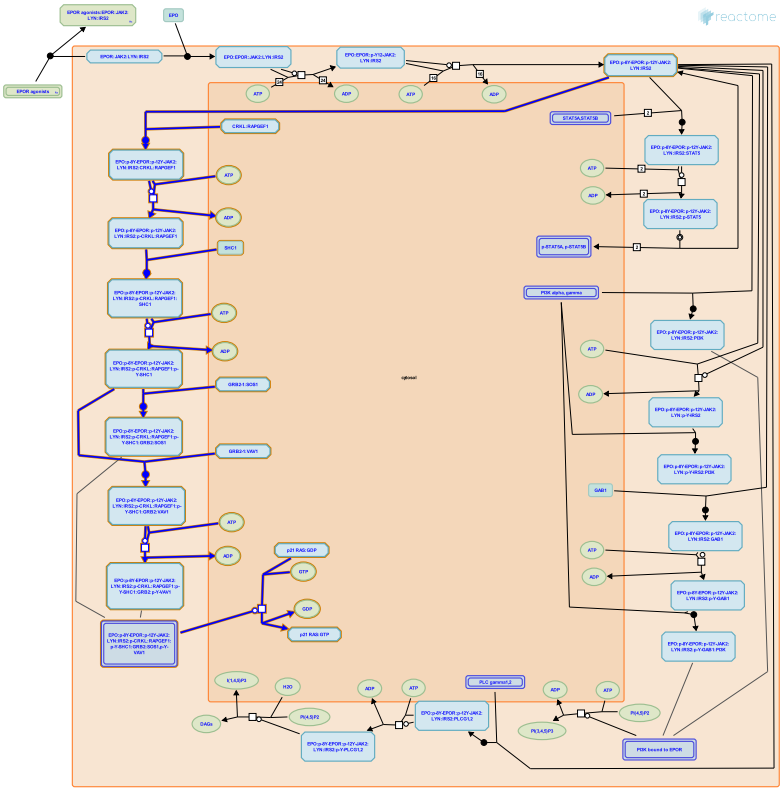
Edit history

Date	Action	Author
2006-05-18	Created	Jassal B
2006-10-10	Authored	Castagnoli L
2008-02-12	Reviewed	Heldin CH
2023-03-15	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35968	P29353			

24. Erythropoietin activates RAS (R-HSA-9027284)



The RAS guanine nucleotide exchange factors SOS1 and VAV1 bind indirectly to the phosphorylated EPOR via CRKL, SHC1, and GRB2 (Miura et al. 1994, Hanazono et al. 1996, Odai et al. 1997, Arai et al. 2001, reviewed in Kuhrt et al. 2015) . The phosphorylated cytoplasmic domain of EPOR binds CRKL, which is then phosphorylated (Arai et al. 2001). Phosphorylated CRKL binds SHC1, which is then phosphorylated and binds either GRB2:SOS1 (Barber et al. 1997) or GRB2:VAV1 (Hanazono et al. 1996). SOS1 and phosphorylated VAV1 catalyze the exchange of GDP for GTP bound to RAS, that is, RAS:GDP is converted to RAS:GTP.

References

Corless CN, Xia K, Roberts TM, D'Andrea AD & Barber DL (1997). Erythropoietin activates Raf1 by an Shc-independent pathway in CTLL-EPO-R cells. Blood, 89, 55-64.

Wojchowski DM & Kuhrt D (2015). Emerging EPO and EPO receptor regulators and signal transducers. Blood, 125, 3536-41.

Yazaki Y, Hanazono Y, Odai H, Hirai H, Sasaki K & Iwamatsu A (1996). Proto-oncogene products Vav and c-Cbl are involved in the signal transduction through Grb2/Ash in hematopoietic cells. Acta Haematol., 95, 236-42.

Arai A, Miura O, Nosaka Y, Kanda E & Miyasaka N (2001). CrkL is recruited through its SH2 domain to the erythropoietin receptor and plays a role in Lyn-mediated receptor signaling. J. Biol. Chem., 276, 33282-90.

Yazaki Y, Hanazono Y, Odai H, Iwamatu A, Hirai H & Sasaki K (1997). The signal transduction through Grb2/Ash in hematopoietic cells. Leukemia, 11, 405-7.

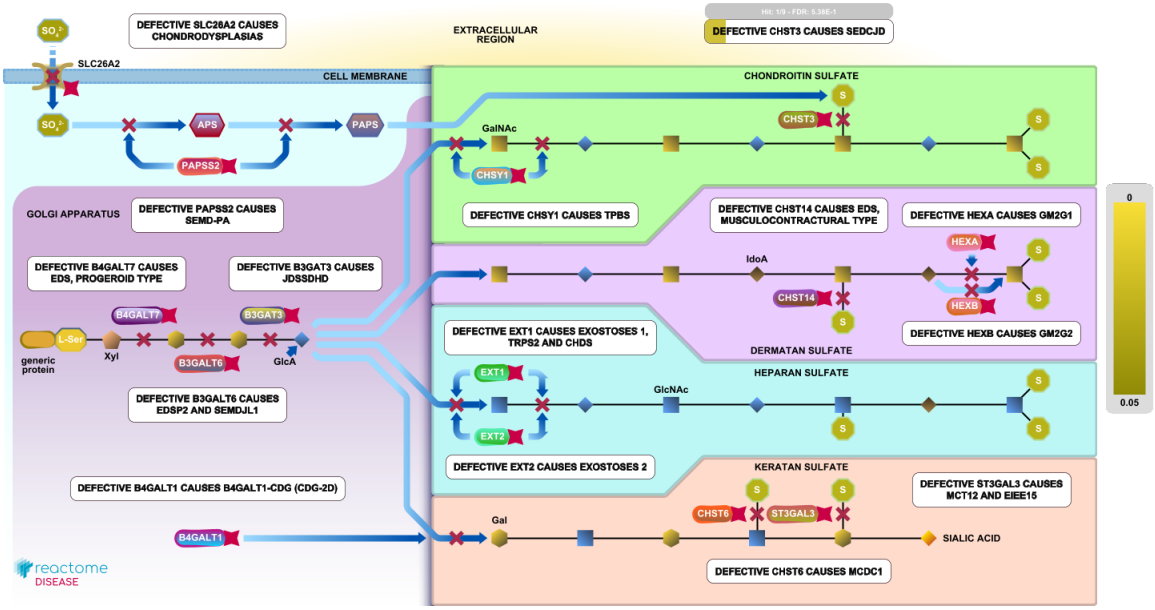
Edit history

Date	Action	Author
2017-10-29	Edited	May B
2017-10-29	Authored	May B
2017-10-29	Created	May B
2018-08-14	Reviewed	McGraw KL
2023-03-15	Modified	Wright A

Interactors found in this pathway (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
KDR	P35968	P29353			

25. Diseases associated with glycosaminoglycan metabolism (R-HSA-3560782)



Diseases: congenital disorder of glycosylation.

A number of genetic disorders are caused by mutations in the genes encoding glycosyltransferases and sulfotransferases, enzymes responsible for the synthesis of glycosaminoglycans (GAGs) as well as hexosaminidase degradation of GAGs (Mizumoto et al. 2013).

References

Sugahara K, Ikegawa S & Mizumoto S (2013). Human genetic disorders caused by mutations in genes encoding biosynthetic enzymes for sulfated glycosaminoglycans. J. Biol. Chem., 288, 10953-61.

Edit history

Date	Action	Author
2013-05-21	Edited	Jassal B
2013-05-21	Authored	Jassal B
2013-05-21	Created	Jassal B
2014-07-09	Reviewed	Spillmann D
2021-11-10	Modified	Matthews L

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

Input	UniProt Id
CHST3	Q7LGC8

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.

15 of the submitted entities were found, mapping to 20 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ARHGEF26	Q96DR7	BTNL8	Q6UX41	CD300LG	Q6UXG3, Q8TDQ1
CHST3	Q7LGC8	COL21A1	Q96P44	CYS1	Q717R9
DPYS	Q14117	GABRB2	P47870	H1-3	P16402
KDR	P35968	OR13G1	Q8NGZ3	OR6N2	Q8NGY6
PDCD1	Q15116	RSPO1	Q2MKA7	SNCB	Q16143

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
OR13G1	ENSG00000197437	OR6N2	ENSG00000188340	SNCB	ENSG00000074317

Interactors (10)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
ARHGEF26	Q96DR7	O14936	BTNL8	Q6UX41-6	O00501
C12orf50	Q8NA57	Q08379	C16orf92	Q96LL3	Q8IY26
CLK2	P49760	Q15696	DPYS	Q14117	Q14957
KDR	P35918	P08581	PDCD1	Q15116	Q06124
PTP4A3	O75365	Q12974	SNCB	Q16143	O75925

7. Identifiers not found

These 26 identifiers were not found neither mapped to any entity in Reactome.

BICDL2	C3orf70	EVPLL	IGHV1-18	IGHV3-21	LINC01018	LINC02232	LINC02591
LOC101927040	LOC101927657	LOC101927668	LOC101929141	LOC440300	LOC93463	MIR23A	MIR3128
MIR6800	MIR942	P4HA3-AS1	PI15	RNU6-31P	RPS7P5	SPDEF	SRPX2
VTRNA1-1	WFDC1						