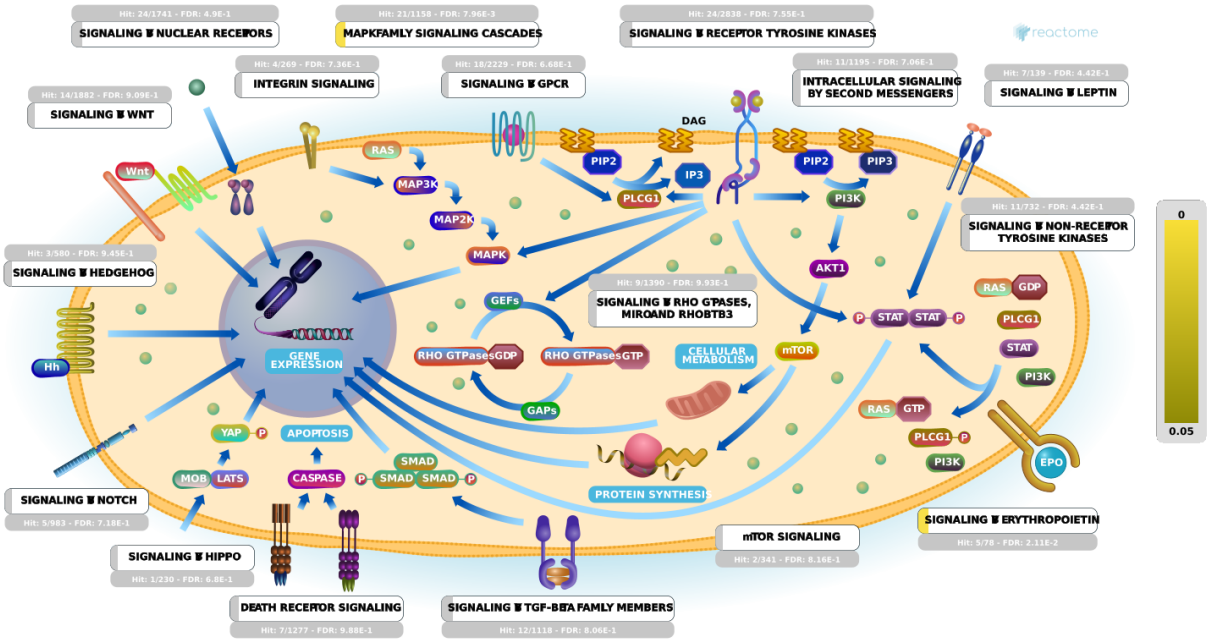
Signal Transduction



Barroso, I., Bevan, AP., Bockaert, J., Charalambous, M., D'Eustachio, P., Garapati, P V., Gillespie, ME., Gonzalez-Perez, RR., Gopinathrao, G., Jassal, B., Joshi-Tope, G., Joutel, A., Jupe, S., Kimelman, D., Liu, Y C., Matthews, L., May, B., McGraw, KL., Orlic-Milacic, M., Pop, C., Roskoski, R Jr., Rothfels, K., Rush, MG., Salvesen, GS., Scherer, T., Shattil, SJ., Stanley, FM., Sudol, M., Vaux, DL., Zwartkruis, FJ.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

01/09/2022

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 81

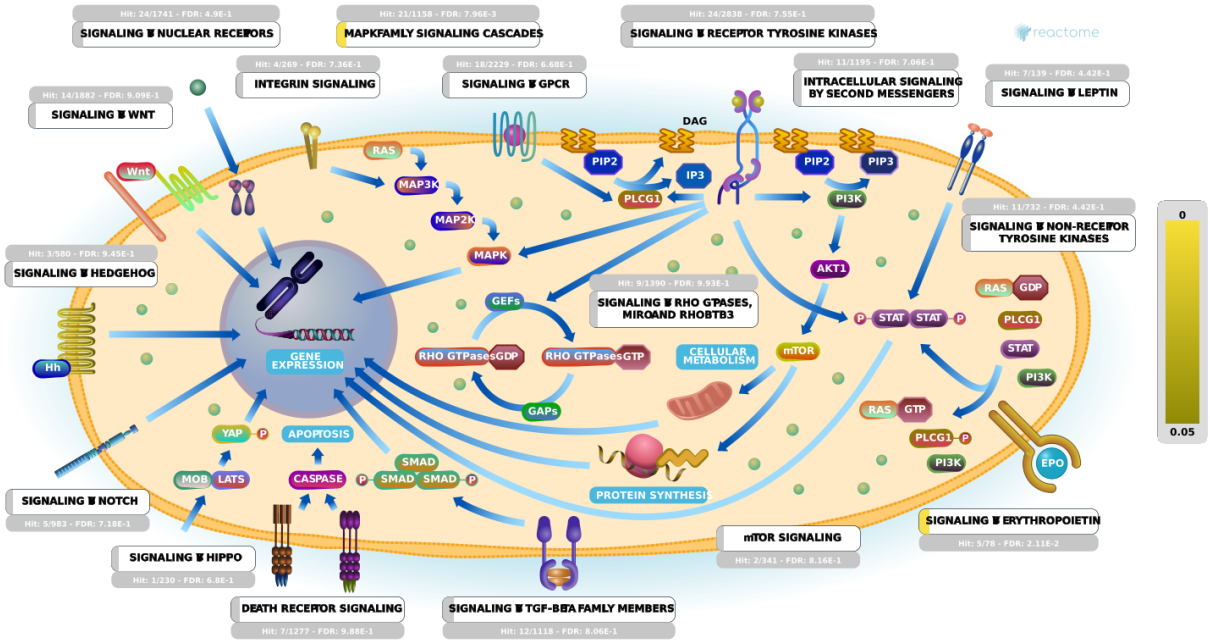
This document contains 18 pathways (see Table of Contents)

Analysis 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. See more
- 39 out of 39 identifiers in the sample were found in Reactome, where 1141 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 MjAyMjA5MDEwNDA3MzZfMzEyNTc%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

Signal Transduction ↗

Stable identifier: R-HSA-162582



Signal transduction is a process in which extracellular signals elicit changes in cell state and activity. Transmembrane receptors sense changes in the cellular environment by binding ligands, such as hormones and growth factors, or reacting to other types of stimuli, such as light. Stimulation of transmembrane receptors leads to their conformational change which propagates the signal to the intracellular environment by activating downstream signaling cascades. Depending on the cellular context, this may impact cellular proliferation, differentiation, and survival. On the organism level, signal transduction regulates overall growth and behavior.

Receptor tyrosine kinases (RTKs) transmit extracellular signals by phosphorylating their protein partners on conserved tyrosine residues. Some of the best studied RTKs are EGFR (reviewed in Avraham and Yarden, 2011), FGFR (reviewed in Eswarakumar et al, 2005), insulin receptor (reviewed in Saltiel and Kahn, 2001), NGF (reviewed in Reichardt, 2006), PDGF (reviewed in Andrae et al, 2008) and VEGF (reviewed in Xie et al, 2004). RTKs frequently activate downstream signaling through RAF/MAP kinases (reviewed in McKay and Morrison, 2007 and Wellbrock et al 2004), AKT (reviewed in Manning and Cantley, 2007) and PLC- gamma (reviewed in Patterson et al, 2005), which ultimately results in changes in gene expression and cellular metabolism.

Receptor serine/threonine kinases of the TGF-beta family, such as TGF-beta receptors (reviewed in Kang et al. 2009) and BMP receptors (reviewed in Miyazono et al. 2009), transmit extracellular signals by phosphorylating regulatory SMAD proteins on conserved serine and threonine residues. This leads to formation of complexes of regulatory SMADs and SMAD4, which translocate to the nucleus where they act as transcription factors.

WNT receptors transmit their signal through beta-catenin. In the absence of ligand, beta-catenin is constitutively degraded in a ubiquitin-dependent manner. WNT receptor stimulation releases beta-catenin from the destruction complex, allowing it to translocate to the nucleus where it acts as a transcriptional regulator (reviewed in MacDonald et al, 2009 and Angers and Moon, 2009). WNT receptors were originally classified as G-protein coupled receptors (GPCRs). Although they are structurally related, GPCRs primarily transmit their signals through G-proteins, which are trimers of alpha, beta and gamma sub-

units. When a GPCR is activated, it acts as a guanine nucleotide exchange factor, catalyzing GDP to GTP exchange on the G-alpha subunit of the G protein and its dissociation from the gamma-beta heterodimer. The G-alpha subunit regulates the activity of adenylate cyclase, while the gamma-beta heterodimer can activate AKT and PLC signaling (reviewed in Rosenbaum et al. 2009, Oldham and Hamm 2008, Ritter and Hall 2009).

NOTCH receptors are activated by transmembrane ligands expressed on neighboring cells, which results in cleavage of NOTCH receptor and release of its intracellular domain. NOTCH intracellular domain translocates to the nucleus where it acts as a transcription factor (reviewed in Kopan and Ilagan, 2009).

Integrins are activated by extracellular matrix components, such as fibronectin and collagen, leading to conformational change and clustering of integrins on the cell surface. This results in activation of integrin-linked kinase and other cytosolic kinases and, in co-operation with RTK signaling, regulates survival, proliferation and cell shape and adhesion (reviewed in Hehlgans et al, 2007) .

Besides inducing changes in gene expression and cellular metabolism, extracellular signals that trigger the activation of Rho GTP-ases can trigger changes in the organization of cytoskeleton, thereby regulating cell polarity and cell-cell junctions (reviewed in Citi et al, 2011).

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McKay, MM., Morrison, DK. (2007). Integrating signals from RTKs to ERK/MAPK. *Oncogene, 26*, 3113-21. ↗

Oldham, WM., Hamm, HE. (2008). Heterotrimeric G protein activation by G-protein-coupled receptors. *Nat Rev Mol Cell Biol, 9*, 60-71. ↗

Editions

2005-05-06	Authored	Gopinathrao, G., Bevan, AP., Charalambous, M., Joshi-Tope, G., Orlic-Milacic, M., Rothfels, K.
2022-05-18	Reviewed	Rush, MG., Barroso, I., Joutel, A., Stanley, FM.

24 submitted entities found in this pathway, mapping to 31 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BAX	Q07812	BCL2	P10415	BRAF	P15056
CXCR1	P25024	CXCR2	P25024, P25025	EGFR	P00533, P04626
IL2	P60568	IL5	P05113	IL6	P05231
IL8	P10145	JAK1	P23458	JAK2	O60674
JAK3	P52333	KRAS	P01116, P01116-1, P01116-2	MAPK	P28482
Myc	P01106	NFKB1	P19838	PARP1	P09874
PIK3CA	P42336	STAT3	P40763	TNF	P01375
WNT1	P04628	WNT6	Q9Y6F9	p53	P04637

Input	Ensembl Id	Input	Ensembl Id
BCL2	ENSG00000171791	Myc	ENSG00000136997, ENST00000377970

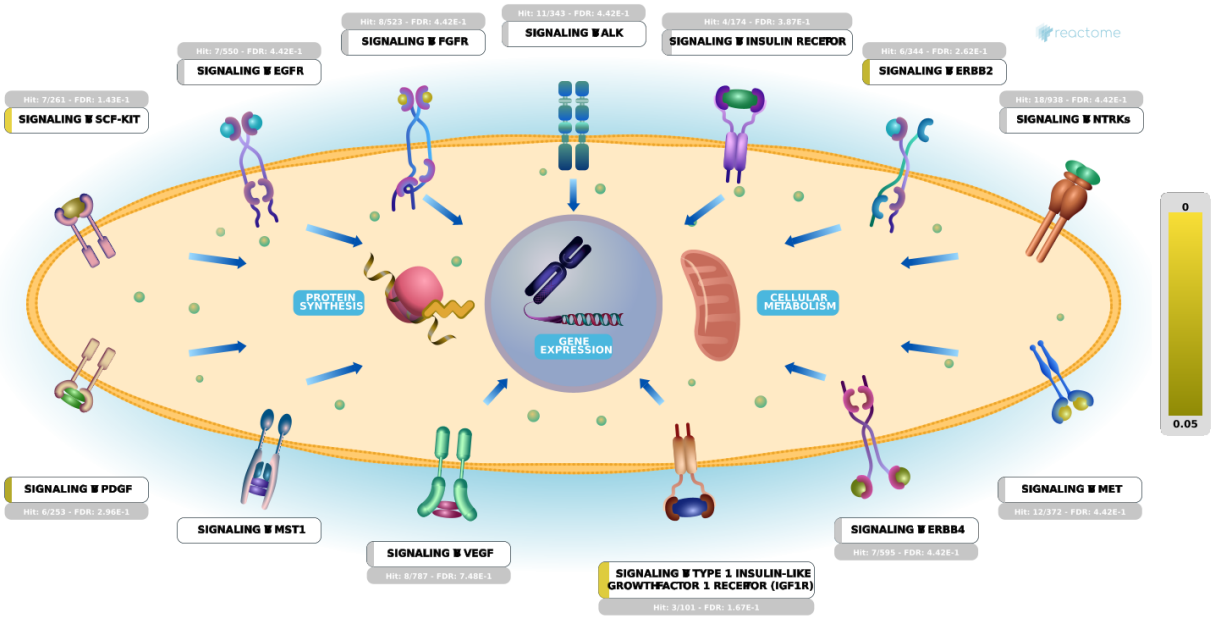
Interactors found in the analysis (24)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BAX	Q07812, Q07813-1	Q07817, P10415, O43521, Q07812	BCL2	P10415	P22736, Q92934, P10415, O43521, P28482, Q07812
BRAF	P15056	P04049, P36507, P15056, P31946, Q02750, P63104	BRCA1	P38398	P24385, Q8WX92, P52292, P62136, Q7Z569
BRCA2	P51587	P09874	CXCR2	P25025	P10145
EGFR	P00533-4, P00533	P25098, Q14247, P35813, P07900, P19174, P12931, P15498, Q05209, P46109, Q99962, Q99963, Q96JA1, O14544, Q13480, O14543, P27986, P46108, P40763, P04049, Q13322, Q68CZ2, P46934, P16234, Q99952, Q05513, P41240, P00533, P29353, P22681, P30307, P32121, P29350, Q06124, Q03135, Q99075, Q05397, P08581, P17252, P23528, Q07889, Q9UQB8, Q99704, P63104, P01135, P42685, P01133, Q9UGK3, P31946, Q14956, Q12933, P18031, P31749, Q13905, P52306, P30530, Q02790, Q9UQC2, Q9UNE7, P00519, P53041, P06493, Q16620, P45983, P04792, Q13153	IL10	P22301	P25490
IL2	IL2	Q13547	IL4	P05112	P31785
IL8	EBI-1566585, P10145	Q92793, P25025	JAK1	P23458	O60674, P40763
JAK2	O60674, Q62120	P46527, O60674, P18031	JAK3	P52333	Q9UNE7
KRAS	P01116, P01116-2, P32883	P04049, P15056, P01116-2, P61586	MUC1	P15941-11, P15941	P01350, P00519, P12931, P00533
Myc	P01106, EBI-1265559	Q8N6T7, O15111, P06307, Q13526, Q13547, Q14839, O43524, Q9Y4A5, P37173, P52292, P08047, O60341, O15169, P49841, P04792, P23771, P40763	NFKB1	P25799-1, P19838-PRO_0000030311, P19838, P25799	Q15788, O15111, Q8IZL8, Q13547, O00255, Q9Y297, P35222, P25963
PARP1	P09874	P22415, Q9NTX7, P09874	PIK3CA	P42336	P27986, P35568, P42336, P01100
STAT	EBI-10952519	P40763	STAT3	EBI-9914958, P40763-2, P40763	P22681, P18031, Q9NP31, Q9UBE8, P12931, O43318, P22736, P43405, Q9NWQ8, P08047, P49137, P00533, P06401, P40763
TNF	P01375	Q15628, O15552, Q12933, Q13546, P01375	p53	P04637, P04637-7, P04637-1	Q09472, Q9Y265, P10415, P29590, Q05397, P22736, P17844, Q92793, O14641, P08047, Q92993, P63104, Q93009, P09874, P49757, Q13526, Q13547, O14980, Q15648, O43524, Q9UHC7, Q06330, Q96ST3, Q00987, P35232, Q15291, P04271, O15169, P49841, P04792, Q15796, Q9UBL3

Signaling by Receptor Tyrosine Kinases ↗

Location: Signal Transduction

Stable identifier: R-HSA-9006934



Receptor tyrosine kinases (RTKs) are a major class of cell surface proteins involved in Signal Transduction. Human cells contain ~60 RTKs, grouped into 20 subfamilies based on their domain architecture. All RTK subfamilies are characterized by an extracellular ligand-binding domain, a single transmembrane region and an intracellular region consisting of the tyrosine kinase domain and additional regulatory and protein interaction domains. In general, RTKs associate into dimers upon ligand binding and are activated by autophosphorylation on conserved intracellular tyrosine residues. Autophosphorylation increases the catalytic efficiency of the receptor and provides binding sites for the assembly of downstream signaling complexes (reveiwed in Lemmon and Schlessinger, 2010). Common signaling pathways activated downstream of RTK activation include RAF/MAP kinase cascades (reviewed in McKay and Morrison, 2007 and Wellbrock et al 2004), AKT signaling (reviewed in Manning and Cantley, 2007) and PLC-gamma mediated signaling (reviewed in Patterson et al). Activation of these pathways ultimately results in changes in gene expression and cellular metabolism.

Literature references

Snyder, SH., Nikolaidis, N., van Rossum, DB., Gill, DL., Patterson, RL. (2005). Phospholipase C-gamma: diverse roles in receptor-mediated calcium signaling. *Trends Biochem Sci, 30*, 688-97. ↗

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Schlessinger, J., Lemmon, MA. (2010). Cell signaling by receptor tyrosine kinases. *Cell, 141*, 1117-34. ↗

Editions

2017-05-24	Authored, Edited	Rothfels, K.
2017-06-22	Reviewed	D'Eustachio, P.

10 submitted entities found in this pathway, mapping to 12 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BAX	Q07812	BRAF	P15056	EGFR	P00533, P04626
JAK2	O60674	JAK3	P52333	KRAS	P01116-1, P01116-2
MAPK	P28482	Myc	P01106	PIK3CA	P42336
STAT3	P40763				

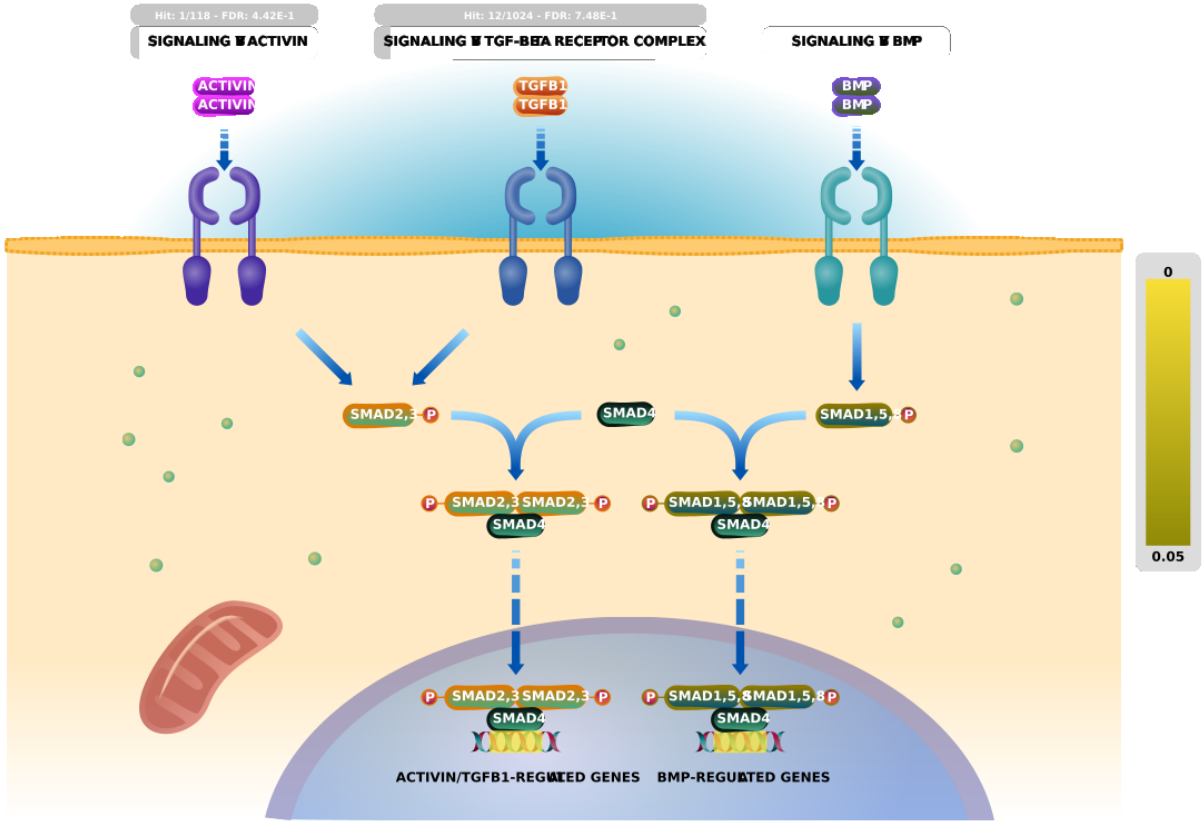
Interactors found in the analysis (16)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BAX	Q07812	Q07812	BCL2	P10415	Q07812
BRAF	P15056	P15056	BRCA1	P38398	Q8WX92
EGFR	P00533-4, P00533	P07900, P29353, P22681, P19174, P29350, Q06124, Q03135, P12931, Q05397, P15498, Q05209, P46109, Q99962, Q99963, P08581, P17252, Q07889, Q9UQB8, Q96JA1, O14544, Q13480, P27986, P46108, P40763, P01133, Q13322, Q68CZ2, P31749, Q13905, P30530, Q9UQC2, Q9UNE7, P46934, P16234, Q99952, P41240, Q16620, P00533, P04792	IL4	P05112	P31785
JAK1	P23458	O60674, P40763	JAK2	O60674	O60674
JAK3	P52333	Q9UNE7	KRAS	P01116	P15056, P61586
MUC1	P15941	P12931, P00533	Myc	EBI-1265559, P01106	Q14839, P04792, P40763
PIK3CA	P42336	P27986, P35568, P42336	STAT	EBI-10952519	P40763
STAT3	EBI-9914958, P40763-2, P40763	P22681, Q9NWQ8, Q9NP31, P49137, P12931, P00533, P06401, P40763	p53	P04637	Q96ST3, Q09472, P04271, P04792, Q05397

Signaling by TGFB family members ↗

Location: Signal Transduction

Stable identifier: R-HSA-9006936



The human genome encodes 33 TGF-beta family members, including TGF-beta itself, as well as bone morphogenetic protein (BMP), activin, nodal and growth and differentiation factors (GDFs). This superfamily of ligands generally binds as dimers to hetero-tetrameric cell-surface receptor serine/threonine kinases to activate SMAD-dependent and SMAD-independent signaling (reviewed in Morikawa et al, 2016; Budi et al, 2017).

Signaling by the TGF-beta receptor complex is initiated by TGF-beta. TGF-beta (TGFB1), secreted as a homodimer, binds to TGF-beta receptor II (TGFBR2), inducing its dimerization and formation of a stable hetero-tetrameric complex with TGF-beta receptor I homodimer (TGFBR1). TGFBR2-mediated phosphorylation of TGFBR1 triggers internalization of the heterotetrameric TGF beta receptor complex (TGFBR) into clathrin coated endocytic vesicles and recruitment of cytosolic SMAD2 and SMAD3, which act as R-SMADs for TGF beta receptor complex. TGFBR1 phosphorylates SMAD2 and SMAD3, promoting their association with SMAD4 (known as Co-SMAD). In the nucleus, the SMAD2/3:SMAD4 heterotrimer binds target DNA elements and, in cooperation with other transcription factors, regulates expression of genes involved in cell differentiation. For a review of TGF-beta receptor signaling, please refer to Kang et al. 2009.

Signaling by BMP is triggered by bone morphogenetic proteins (BMPs). BMPs can bind type I receptors in the absence of type II receptors, but the presence of both types dramatically increases binding affinity. The type II receptor kinase transphosphorylates the type I receptor, leading to recruitment and phosphorylation of SMAD1, SMAD5 and SMAD8, which function as R-SMADs in BMP signalling pathways. Phosphorylated SMAD1, SMAD5 and SMAD8 form heterotrimeric complexes with SMAD4, the only Co-SMAD in mammals. The SMAD1/5/8:SMAD4 heterotrimer regulates transcription of genes involved in de-

velopment of many tissues, including bone, cartilage, blood vessels, heart, kidney, neurons, liver and lung. For review of BMP signaling, please refer to Miyazono et al. 2010.

Signaling by activin is triggered when an activin dimer (activin A, activin AB or activin B) binds the type II receptor (ACVR2A, ACVR2B). This complex then interacts with the type I receptor (ACVR1B, ACVR1C) and phosphorylates it. The phosphorylated type I receptor phosphorylates SMAD2 and SMAD3. Dimers of phosphorylated SMAD2/3 bind SMAD4 and the resulting ternary complex enters the nucleus and activates target genes. For a review of activin signaling, please refer to Chen et al. 2006.

Literature references

Kang, JS., Derynck, R., Liu, C. (2009). New regulatory mechanisms of TGF-beta receptor function. *Trends Cell Biol, 19*, 385-94. ↗

Miyazono, K., Kamiya, Y., Morikawa, M. (2010). Bone morphogenetic protein receptors and signal transduction. *J Biochem, 147*, 35-51. ↗

Miyazono, K., Derynck, R., Morikawa, M. (2016). TGF-β and the TGF-β Family: Context-Dependent Roles in Cell and Tissue Physiology. *Cold Spring Harb Perspect Biol, 8*. ↗

Derynck, R., Duan, D., Budi, EH. (2017). Transforming Growth Factor-β Receptors and Smads: Regulatory Complexity and Functional Versatility. *Trends Cell Biol.*. ↗

Chuang, J., Chang, CD., Chung, J., Wang, Q., Chen, YG., Lin, SL. et al. (2006). Activin signaling and its role in regulation of cell proliferation, apoptosis, and carcinogenesis. *Exp. Biol. Med. (Maywood), 231*, 534-44. ↗

Editions

2017-05-24	Authored, Edited	Rothfels, K.
2017-06-22	Reviewed	D'Eustachio, P.

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
MAPK	P28482	Myc	P01106	PARP1	P09874

Input	Ensembl Id
Myc	ENSG00000136997

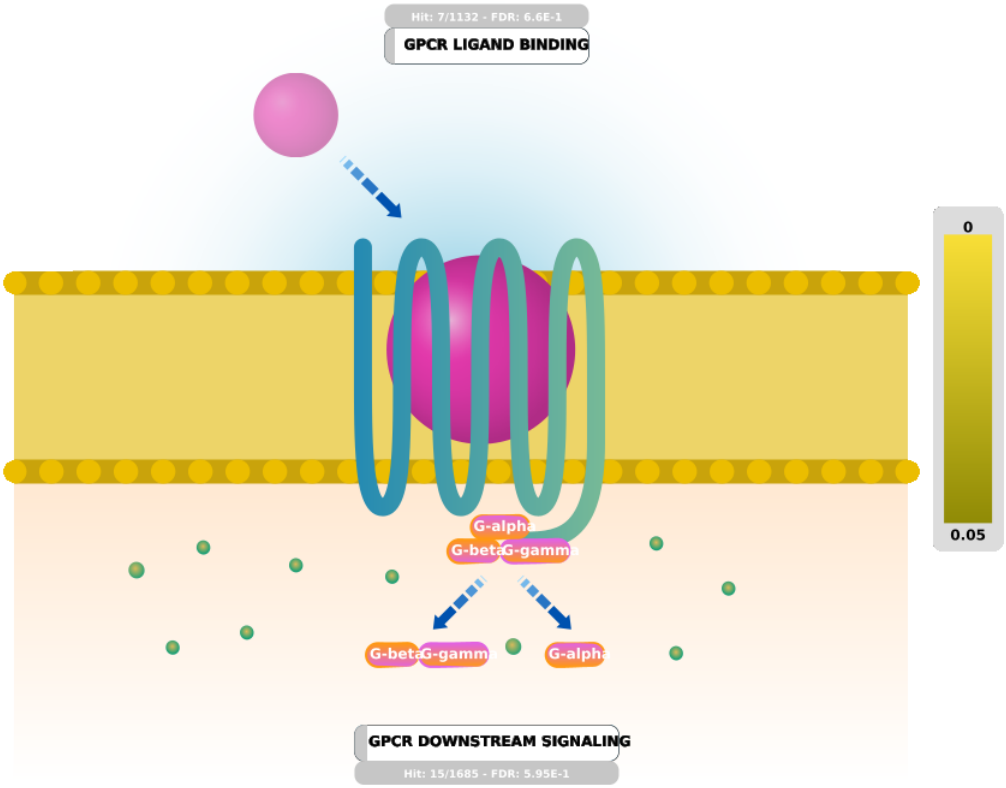
Interactors found in the analysis (9)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BRCA2	P51587	P09874	EGFR	P00533	Q9UNE7, P35813, P22681
IL2	IL2	Q13547	JAK3	P52333	Q9UNE7
Myc	P01106	P37173, Q13547, P08047	NFKB1	P19838-PRO_0000030311, P19838	Q13547, O00255
PARP1	P09874	P09874	STAT3	P40763	P22681, P08047
p53	P04637	Q09472, Q13547, O14980, P08047, Q15796, P09874			

Signaling by GPCR ↗

Location: Signal Transduction

Stable identifier: R-HSA-372790



G protein-coupled receptors (GPCRs; 7TM receptors; seven transmembrane domain receptors; heptahelical receptors; G protein-linked receptors [GPLR]) are the largest family of transmembrane receptors in humans, accounting for more than 1% of the protein-coding capacity of the human genome. All known GPCRs share a common architecture of seven membrane-spanning helices connected by intra- and extracellular loops. The extracellular loops contain two highly-conserved cysteine residues that form disulphide bonds to stabilize the structure of the receptor. They recognize diverse messengers such as light, odorants, small molecules, hormones and neurotransmitters. Most GPCRs act as guanine nucleotide exchange factors; activated by ligand binding, they promote GDP-GTP exchange on associated heterotrimeric guanine nucleotide-binding (G) proteins. There are two models for GPCR-G Protein interactions: 1) ligand-GPCR binding first, then binding to G Proteins; 2) "Pre-coupling" of GPCRs and G Proteins before ligand binding (review Oldham WM and Hamm HE, 2008). These in turn activate effector enzymes or ion channels. GPCRs are involved in a range of physiological roles which include the visual sense, smell, behavioural regulation, functions of the autonomic nervous system and regulation of the immune system and inflammation.

GPCRs are divided into classes based on sequence homology and functional similarity. The main mammalian classes, in order of size, are the Rhodopsin-like family A, the Secretin receptor family B, and the Metabotropic glutamate/pheromone receptor family C.

Literature references

Bockaert, J., Pin, JP. (1999). Molecular tinkering of G protein-coupled receptors: an evolutionary success. *EMBO J, 18* , 1723-9. ↗

Oldham, WM., Hamm, HE. (2008). Heterotrimeric G protein activation by G-protein-coupled receptors. *Nat Rev Mol Cell Biol, 9*, 60-71. ↗

Bouhelal, R., Jacoby, E., Gerspacher, M., Seuwen, K. (2006). The 7 TM G-protein-coupled receptor target family. *ChemMedChem, 1*, 761-82. ↗

Editions

2008-07-02	Authored	Jassal, B.
2008-09-01	Reviewed	Bockaert, J.
2008-09-01	Edited	D'Eustachio, P.

9 submitted entities found in this pathway, mapping to 11 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
CXCR1	P25024	CXCR2	P25024, P25025	EGFR	P00533
IL8	P10145	KRAS	P01116-1, P01116-2	MAPK	P28482
PIK3CA	P42336	WNT1	P04628	WNT6	Q9Y6F9

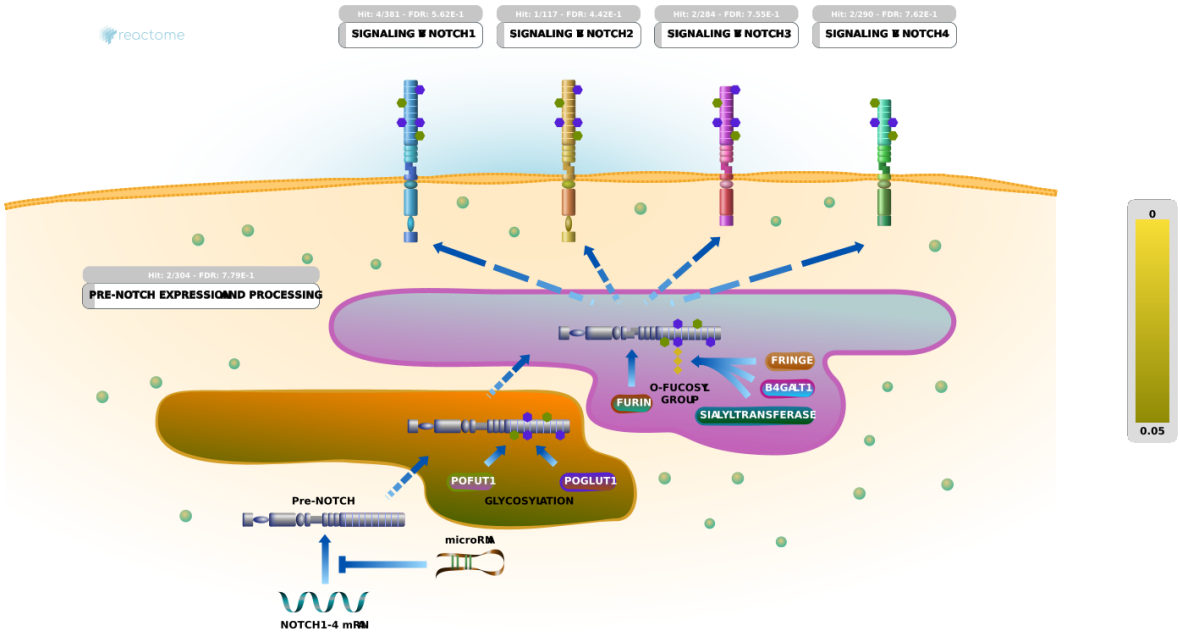
Interactors found in the analysis (10)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BCL2	P10415	P28482	BRCA1	P38398	P52292, P62136
CXCR2	P25025	P10145	EGFR	P00533	P25098, P17252, P00533, P12931, Q99075, Q13153
IL8	P10145	P25025	KRAS	P01116	P61586
MUC1	P15941-11, P15941	P01350, P00533, P12931	Myc	P01106	P06307, P52292
STAT3	P40763	P00533, P12931	TNF	P01375	O15552

Signaling by NOTCH ↗

Location: Signal Transduction

Stable identifier: R-HSA-157118



The Notch Signaling Pathway (NSP) is a highly conserved pathway for cell-cell communication. NSP is involved in the regulation of cellular differentiation, proliferation, and specification. For example, it is utilised by continually renewing adult tissues such as blood, skin, and gut epithelium not only to maintain stem cells in a proliferative, pluripotent, and undifferentiated state but also to direct the cellular progeny to adopt different developmental cell fates. Analogously, it is used during embryonic development to create fine-grained patterns of differentiated cells, notably during neurogenesis where the NSP controls patches such as that of the vertebrate inner ear where individual hair cells are surrounded by supporting cells.

This process is known as lateral inhibition: a molecular mechanism whereby individual cells within a field are stochastically selected to adopt particular cell fates and the NSP inhibits their direct neighbours from doing the same. The NSP has been adopted by several other biological systems for binary cell fate choice. In addition, the NSP is also used during vertebrate segmentation to divide the growing embryo into regular blocks called somites which eventually form the vertebrae. The core of this process relies on regular pulses of Notch signaling generated from a molecular oscillator in the presomatic mesoderm.

The Notch receptor is synthesized in the rough endoplasmic reticulum as a single polypeptide precursor. Newly synthesized Notch receptor is proteolytically cleaved in the trans-golgi network, creating a heterodimeric mature receptor comprising of non-covalently associated extracellular and transmembrane subunits. This assembly travels to the cell surface ready to interact with specific ligands. Following ligand activation and further proteolytic cleavage, an intracellular domain is released and translocates to the nucleus where it regulates gene expression.

Editions

2004-12-15	Authored	Jassal, B.
2004-12-15	Reviewed	Joutel, A.

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
EGFR	P00533	Myc	P01106	p53	P04637

Input	Ensembl Id
Myc	ENSG00000136997

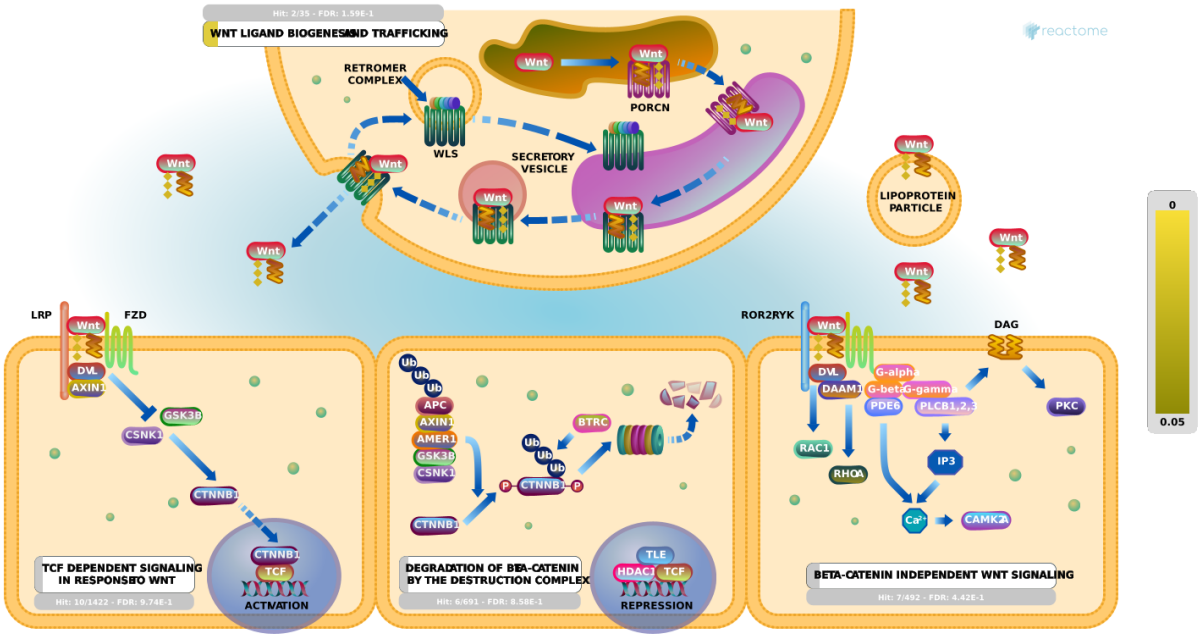
Interactors found in the analysis (4)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	P31749	IL8	EBI-1566585	Q92793
Myc	P01106	Q8N6T7	p53	P04637	Q09472, Q92793, P49757, Q06330

Signaling by WNT ↗

Location: Signal Transduction

Stable identifier: R-HSA-195721



WNT signaling pathways control a wide range of developmental and adult process in metozoans including cell proliferation, cell fate decisions, cell polarity and stem cell maintenance (reviewed in Saito-Diaz et al, 2013; MacDonald et al, 2009). The pathway is named for the WNT ligands, a large family of secreted cysteine-rich glycoproteins. At least 19 WNT members have been identified in humans and mice with distinct expression patterns during development (reviewed in Willert and Nusse, 2012). These ligands can activate at least three different downstream signaling cascades depending on which receptors they engage.

In the so-called 'canonical' WNT signaling pathway, WNT ligands bind one of the 10 human Frizzled (FZD) receptors in conjunction with the LRP5/6 co-receptors to activate a transcriptional cascade that controls processes such as cell fate, proliferation and self-renenwal of stem cells. Engagement of the FZD-LRP receptor by WNT ligand results in the stabilization and translocation of cytosolic beta-catenin to the nucleus where it is a co-activator for LEF (lymphoid enhancer-binding factor)- and TCF (T cell factor) -dependent transcription. In the absence of WNT ligand, cytosolic beta-catenin is phosphorylated by a degradation complex consisting of glycogen synthase kinase 3 (GSK3), casein kinase 1 (CK1), Axin and Adenomatous polyposis coli (APC), and subsequently ubiquitinated and degraded by the 26S proteasome (reviewed in Saito-Diaz et al, 2013; Kimmelman and Xu, 2006).

In addition to the beta-catenin-dependent transcriptional response, WNT signaling can also activate distinct non-transcriptional pathways that regulate cell migration and polarity. These beta-catenin-independent 'non-canonical' pathways signal through Frizzled receptors independently of LRP5/6, or occur through the tyrosine kinase receptors ROR and RYK (reviewed in Veeman et al, 2003; James et al, 2009). Non-canonical WNT pathways are best studied in Drosophila where the planar cell polarity (PCP) pathway controls the orientation of wing hairs and eye facets, but are also involved in processes such as convergent extension, neural tube closure, inner ear development and hair orientation in vertebrates and mammals(reviewed in Seifert and Mlodzik, 2007; Simons and Mlodzik, 2008). In the PCP pathway, binding of WNT ligand to the FZD receptor leads to activation of small Rho GTPases and JNK, which regulate

the cytoskeleton and coordinate cell migration and polarity (reviewed in Lai et al, 2009; Schlessinger et al, 2009). In some cases, a FZD-WNT interaction increases intracellular calcium concentration and activates CaMK II and PKC; this WNT calcium pathway promotes cell migration and inhibits the canonical beta-catenin dependent transcriptional pathway (reviewed in Kuhl et al, 2000; Kohn and Moon, 2005; Rao et al 2010). Binding of WNT to ROR or RYK receptors also regulates cell migration, apparently through activation of JNK or SRC kinases, respectively, however the details of these pathways remain to be worked out (reviewed in Minami et al, 2010).

Although the WNT signaling pathways were originally viewed as discrete, linear pathways controlled by defined subsets of 'canonical' or 'non-canonical' ligands and receptors, the emerging evidence is challenging this notion. Instead, the specificity and the downstream response appear to depend on the particular cellular context and vary with species, tissue and stage of development (reviewed in van Amerongen and Nusse, 2009; Rao et al, 2010).

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Kühl, M., Rao, TP. (2010). An updated overview on Wnt signaling pathways: a prelude for more. *Circ. Res., 106*, 1798-806. ↗

Editions

2007-04-03	Authored	Kimelman, D.
2007-04-03	Edited	Matthews, L.

4 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id	Input	UniProt Id
KRAS	P01116-2	Myc	P01106
WNT1	P04628	WNT6	Q9Y6F9

Input	Ensembl Id
Myc	ENSG00000136997, ENST00000377970

Interactors found in the analysis (8)

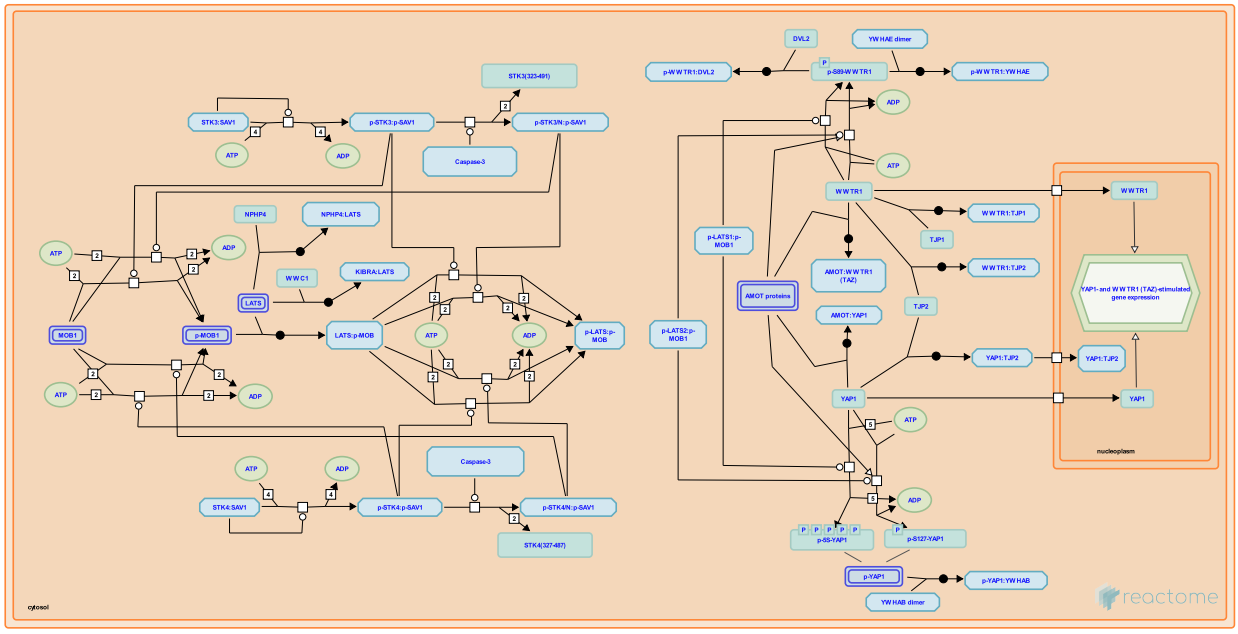
Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BRAF	P15056	P63104	EGFR	P00533	P17252, P32121, P63104
IL2	IL2	Q13547	Myc	P01106	Q9Y4A5, Q13547, O15169, P49841
NFKB1	P19838-PRO_0000030311, P19838	Q13547, O00255, Q9Y297, P35222	PARP1	P09874	Q9NTX7
STAT3	P40763	Q9UBE8, O43318	p53	P04637	Q9Y265, Q13547, O14980, Q15291, O14641, Q92993, O15169, P49841, P63104, Q9UBL3

Signaling by Hippo ↗

Location: Signal Transduction

Stable identifier: R-HSA-2028269

Compartments: cytosol



Human Hippo signaling is a network of reactions that regulates cell proliferation and apoptosis, centered on a three-step kinase cascade. The cascade was discovered by analysis of Drosophila mutations that lead to tissue overgrowth, and human homologues of its components have since been identified and characterized at a molecular level. Data from studies of mice carrying knockout mutant alleles of the genes as well as from studies of somatic mutations in these genes in human tumors are consistent with the conclusion that in mammals, as in flies, the Hippo cascade is required for normal regulation of cell proliferation and defects in the pathway are associated with cell overgrowth and tumorigenesis (Oh and Irvine 2010; Pan 2010; Zhao et al. 2010). This group of reactions is also notable for its abundance of protein:protein interactions mediated by WW domains and PPxY sequence motifs (Sudol and Harvey 2010).

There are two human homologues of each of the three Drosophila kinases, whose functions are well conserved: expression of human proteins rescues fly mutants. The two members of each pair of human homologues have biochemically indistinguishable functions. Autophosphorylated STK3 (MST2) and STK4 (MST1) (homologues of Drosophila Hippo) catalyze the phosphorylation and activation of LATS1 and LATS2 (homologues of Drosophila Warts) and of the accessory proteins MOB1A and MOB1B (homologues of Drosophila Mats). LATS1 and LATS2 in turn catalyze the phosphorylation of the transcriptional co-activators YAP1 and WWTR1 (TAZ) (homologues of Drosophila Yorkie).

In their unphosphorylated states, YAP1 and WWTR1 freely enter the nucleus and function as transcriptional co-activators. In their phosphorylated states, however, YAP1 and WWTR1 are instead bound by 14-3-3 proteins, YWHAB and YWHAE respectively, and sequestered in the cytosol.

Several accessory proteins are required for the three-step kinase cascade to function. STK3 (MST2) and STK4 (MST1) each form a complex with SAV1 (homologue of Drosophila Salvador), and LATS1 and LATS2 form complexes with MOB1A and MOB1B (homologues of Drosophila Mats).

In Drosophila a complex of three proteins, Kibra, Expanded, and Merlin, can trigger the Hippo cascade. A human homologue of Kibra, WWC1, has been identified and indirect evidence suggests that it can reg-

ulate the human Hippo pathway (Xiao et al. 2011). A molecular mechanism for this interaction has not yet been worked out and the molecular steps that trigger the Hippo kinase cascade in humans are unknown.

Four additional processes related to human Hippo signaling, although incompletely characterized, have been described in sufficient detail to allow their annotation. All are of physiological interest as they are likely to be parts of mechanisms by which Hippo signaling is modulated or functionally linked to other signaling processes. First, the caspase 3 protease cleaves STK3 (MST2) and STK4 (MST1), releasing inhibitory carboxyterminal domains in each case, leading to increased kinase activity and YAP1 / TAZ phosphorylation (Lee et al. 2001). Second, cytosolic AMOT (angiomotin) proteins can bind YAP1 and WWTR1 (TAZ) in their unphosphorylated states, a process that may provide a Hippo-independent mechanism to down-regulate the activities of these proteins (Chan et al. 2011). Third, WWTR1 (TAZ) and YAP1 bind ZO-1 and 2 proteins (Remue et al. 2010; Oka et al. 2010). Fourth, phosphorylated WWTR1 (TAZ) binds and sequesters DVL2, providing a molecular link between Hippo and Wnt signaling (Varelas et al. 2010).

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Pawson, T., Wrana, JL., Gregorieff, A., Sakuma, R., Fellouse, FA., Attisano, L. et al. (2010). The Hippo pathway regulates Wnt/beta-catenin signaling. *Dev Cell, 18*, 579-91. ↗

Editions

2011-12-30	Edited	D'Eustachio, P.
2012-02-03	Authored	D'Eustachio, P.
2012-02-03	Reviewed	Sudol, M.

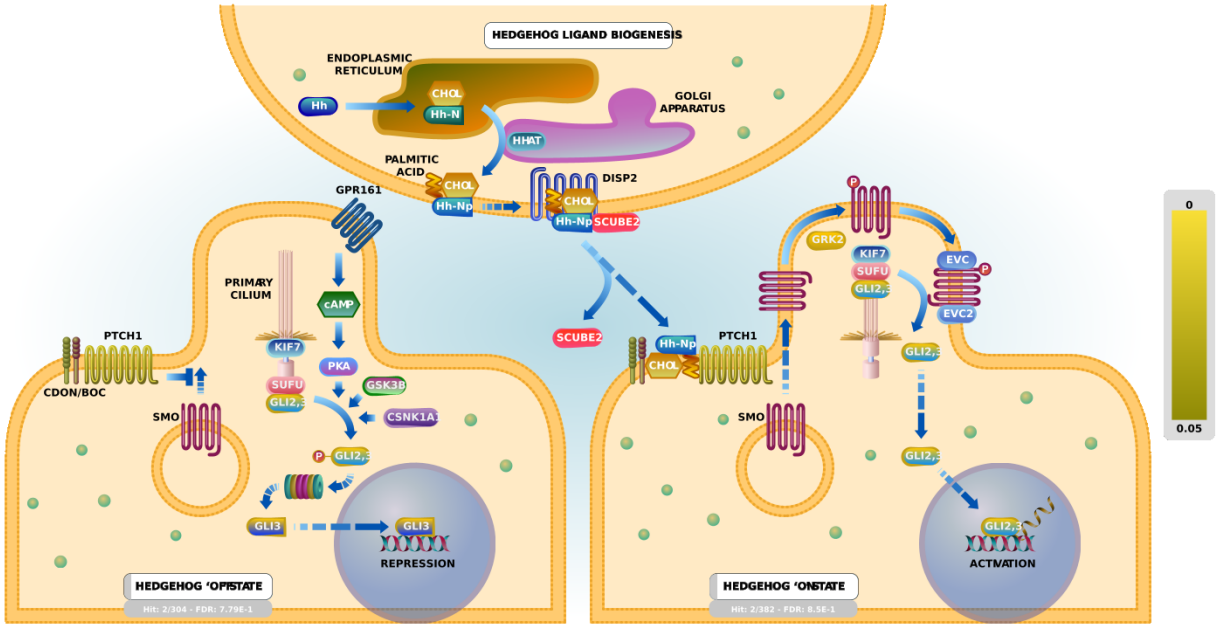
Interactors found in the analysis (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
p53	P04637	O14641			

Signaling by Hedgehog ↗

Location: Signal Transduction

Stable identifier: R-HSA-5358351



Hedgehog (Hh) is a secreted morphogen that regulates developmental processes in vertebrates including limb bud formation, neural tube patterning, cell growth and differentiation (reviewed in Hui and Angers, 2011). Hh signaling also contributes to stem cell homeostasis in adult tissues. Downregulation of Hh signaling can lead to neonatal abnormalities, while upregulation of signaling is associated with the development of various cancers (Beachy et al, 2004; Jiang and Hui, 2008; Hui and Angers, 2011).

Hh signaling is switched between 'off' and an 'on' states to differentially regulate an intracellular signaling cascade that targets the Gli transcription factors. In the absence of Hh ligand, cytosolic Gli proteins are cleaved to yield a truncated form that translocates into the nucleus and represses target gene transcription. Binding of Hh to the Patched (PTC) receptor on the cell surface stabilizes the Gli proteins in their full-length transcriptional activator form, stimulating Hh-dependent gene expression (reviewed in Hui and Angers, 2011; Briscoe and Therond, 2013).

Literature references

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Berman, DM., Beachy, PA., Karhadkar, SS. (2004). Tissue repair and stem cell renewal in carcinogenesis. *Nature, 432*, 324-31. ↗

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Editions

2014-03-24	Authored	Rothfels, K.
2014-04-20	Edited	D'Eustachio, P.
2014-05-16	Reviewed	Liu, Y C.

Interactors found in the analysis (3)

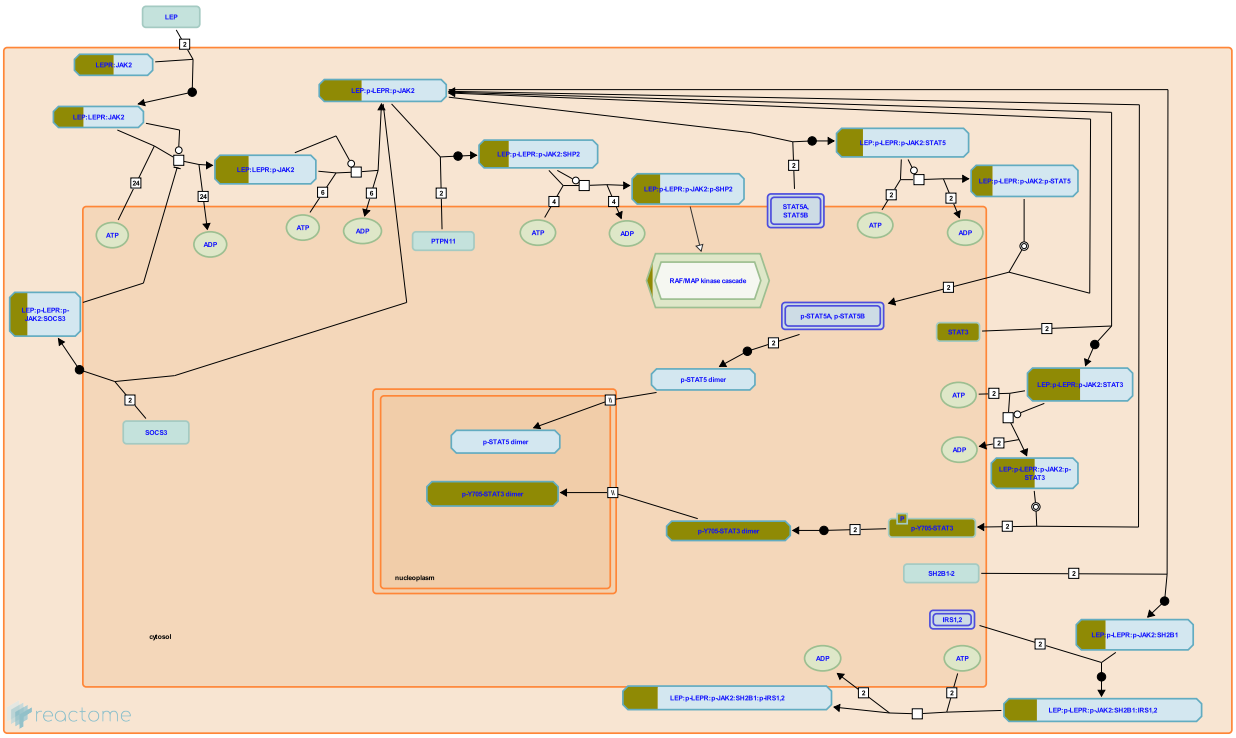
Input	UniProt Id	Interacts with
EGFR	P00533	P25098
p53	P04637	P49841, P49757
Myc	P01106	P49841

Signaling by Leptin ↗

Location: Signal Transduction

Stable identifier: R-HSA-2586552

Compartments: cytosol, plasma membrane



Leptin (LEP, OB, OBS), a circulating adipokine, and its receptor LEPR (DB, OBR) control food intake and energy balance and are implicated in obesity-related diseases (recently reviewed in Amitani et al. 2013, Dunmore and Brown 2013, Cottrell and Mercer 2012, La Cava 2012, Marroqui et al. 2012, Paz-Filho et al. 2012, Denver et al. 2011, Lee 2011, Marino et al. 2011, Morton and Schwartz 2011, Scherer and Buettner 2011, Shan and Yeo 2011, Wauman and Tavernier 2011, Dardeno et al. 2010, Bjorbaek 2009, Morris and Rui 2009, Myers et al. 2008), including cancer (Guo et al. 2012), inflammation (Newman and Gonzalez-Perez 2013, Iikuni et al. 2008), and angiogenesis (Gonzalez-Perez et al. 2013).

The identification of spontaneous mutations in the leptin gene (ob or LEP) and the leptin receptor gene (Ob-R, db or LEPR) genes in mice opened up a new field in obesity research. Leptin was discovered as the product of the gene affected by the ob (obesity) mutation, which causes obesity in mice. Likewise LEPR is the product of the gene affected by the db (diabetic) mutation. Leptin binding to LEPR induces canonical (JAK2/STATs; MAPK/ERK 1/2, PI-3K/AKT) and non-canonical signaling pathways (PKC, JNK, p38 MAPK and AMPK) in diverse cell types. The binding of leptin to the long isoform of LEPR (OB-Rl) initiates a phosphorylation cascade that results in transcriptional activation of target genes by STAT5 and STAT3 and activation of the PI3K pathway(not shown here), the MAPK/ERK pathway, and the mTOR/S6K pathway. Shorter LEPR isoforms with truncated intracellular domains are unable to activate the STAT pathway, but can transduce signals by way of activation of JAK2, IRS-1 or ERKs, including MAPKs.

LEPR is constitutively bound to the JAK2 kinase. Binding of LEP to LEPR causes a conformational change in LEPR that activates JAK2 autophosphorylation followed by phosphorylation of LEPR by JAK2. Phosphorylated LEPR binds STAT3, STAT5, and SHP2 which are then phosphorylated by JAK2. Phosphorylated JAK2 binds SH2B1 which then binds IRS1/2, resulting in phosphorylation of IRS1/2 by JAK2. Phosphorylated STAT3 and STAT5 dimerize and translocate to the nucleus where they activate transcrip-

tion of target genes (Jovanovic et al. 2010). SHP2 activates the MAPK pathway. IRS1/2 activate the PI3K/AKT pathway which may be the activator of mTOR/S6K.

Several isoforms of LEPR have been identified (reviewed in Gorska et al. 2010). The long isoform (LEPRb, OBRb) is expressed in the hypothalamus and all types of immune cells. It is the only isoform known to fully activate signaling pathways in response to leptin. Shorter isoforms (LEPRa, LEPRc, LEPRd, and a soluble isoform LEPRe) are able to interact with JAK kinases and activate other pathways, however their roles in energy homeostasis are not fully characterized.

Literature references

Cowley, MA., Münzberg, H., Myers, MG. (2008). Mechanisms of leptin action and leptin resistance. *Annu. Rev. Physiol., 70*, 537-56.

Gonzalez-Perez, RR., Liu, M., Guo, S., Wang, G., Torroella-Kouri, M. (2012). Oncogenic role and therapeutic target of leptin signaling in breast cancer and cancer stem cells. *Biochim. Biophys. Acta, 1825*, 207-22.

Bonett, RM., Denver, RJ., Boorse, GC. (2011). Evolution of leptin structure and function. *Neuroendocrinology, 94*, 21-38 .

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Iikuni, N., Matarese, G., Lam, QL., Lu, L., La Cava, A. (2008). Leptin and Inflammation. *Curr Immunol Rev, 4*, 70-79.

Editions

2012-11-15	Authored	May, B.
2012-11-24	Edited	May, B.
2013-08-31	Reviewed	Scherer, T.
2013-10-26	Reviewed	Gonzalez-Perez, RR.

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

Input	UniProt Id	Input	UniProt Id
JAK2	O60674	STAT3	P40763

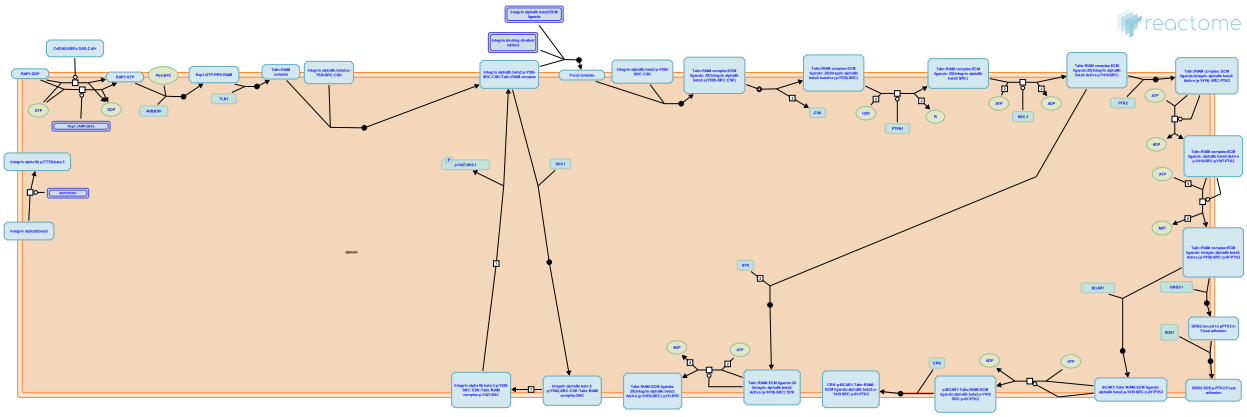
Interactors found in the analysis (5)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	Q06124, O14543, P40763	JAK1	P23458	P40763
Myc	EBI-1265559	P40763	STAT	EBI-10952519	P40763
STAT3	EBI-9914958, P40763	P40763			

Integrin signaling ↗

Location: Signal Transduction

Stable identifier: R-HSA-354192



Integrins are a major family of cell surface receptors that modulate cell adhesion, migration, proliferation and survival through interaction with the extracellular matrix (ECM) and the actin cytoskeleton. Integrins are type 1 transmembrane proteins that exist at the cell surface as heterodimers of alpha and beta subunits, of which there are 18 and 8 different isoforms, respectively, in human cells. In addition to their mechanical role in mediating contact between the ECM and the cytoskeleton, integrins also modulate intracellular signaling pathways governing cytoskeletal rearrangements and pro-survival and mitogenic signaling (reviewed in Hehlgans et al, 2007; Harburger and Calderwood, 2009; Ata and Antonescu, 2017).

In this pathway, we describe signaling through integrin alphaIIb beta3 as a representative example.

At the sites of vascular injury bioactive molecules such as thrombin, ADP, collagen, fibrinogen and thrombospondin are generated, secreted or exposed. These stimuli activate platelets, converting the major platelet integrin alphaIIbbeta3 from a resting state to an active conformation, in a process termed integrin priming or 'inside-out signalling'. Integrin activation refers to the change required to enhance ligand-binding activity. The activated alphaIIbbeta3 interacts with the fibrinogen and links platelets together in an aggregate to form a platelet plug. AlphaIIbbeta3 bound to fibrin generates more intracellular signals (outside-in signalling), causing further platelet activation and platelet-plug retraction.

In the resting state the alpha and beta tails are close together. This interaction keeps the membrane proximal regions in a bent conformation that maintains alphaIIbbeta3 in a low affinity state.

Integrin alphaIIbbeta3 is released from its inactive state by interaction with the protein talin. Talin interacts with the beta3 cytoplasmic domain and disrupts the salt bridge between the alpha and beta chains. This separation in the cytoplasmic regions triggers the conformational change in the extracellular domain that increases its affinity to fibrinogen.

Much of talin exists in an inactive cytosolic pool, and the Rap1 interacting adaptor molecule (RIAM) is implicated in talin activation and translocation to beta3 integrin cytoplasmic domain.

Literature references

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Ata, R., Antonescu, CN. (2017). Integrins and Cell Metabolism: An Intimate Relationship Impacting Cancer. *Int J Mol Sci, 18*. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.
2011-02-13	Revised	Garapati, P V.

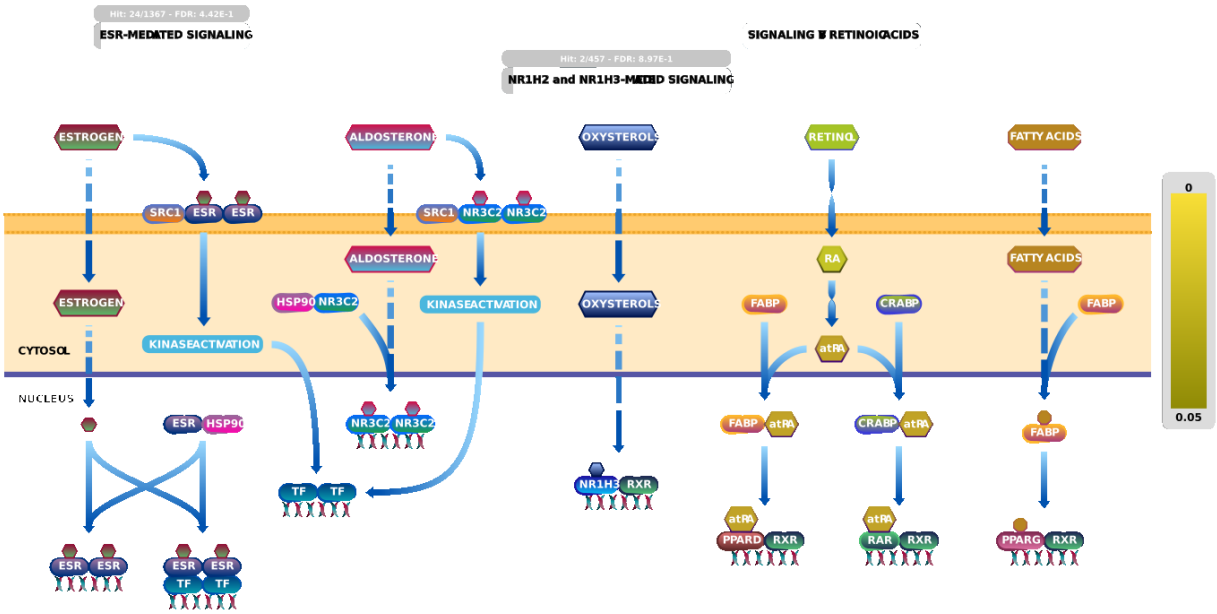
Interactors found in the analysis (4)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	P29353, P41240, P18031, Q07889, P46108, Q05397	JAK2	O60674	P18031
STAT3	P40763	P43405, P18031	p53	P04637	Q05397

Signaling by Nuclear Receptors ↗

Location: Signal Transduction

Stable identifier: R-HSA-9006931



Nuclear receptors (NRs) are ligand-activated transcription factors that bind to small lipid based molecules to regulate gene expression and other cellular process. This family includes receptors for steroid hormones and derivatives (such as estrogen, progesterone, glucocorticoids, Vitamin D, oxysterols and bile acids, among others) as well as receptors for retinoic acids, thyroid hormones and fatty acids and their derivatives. These ligands are able to diffuse directly through cellular membranes as a result of their lipophilic nature (reviewed in Beato et al, 1996; Holzer et al, 2017).

The 48 human nuclear receptors share a conserved modular structure that consists of a sequence specific DNA-binding domain and a ligand-binding domain, in addition to various other protein-protein interaction domains. Upon interaction with ligand, NRs bind to the regulatory regions of target genes as homo- or heterodimers, or more rarely, as monomers. At the promoter, NRs interact with other activators and repressors to regulate gene expression (reviewed Beato et al, 1996; Simons et al, 2014; Hah and Kraus, 2010).

A number of nuclear receptors are cytoplasmic in the absence of ligand and exist as part of a heat shock protein complex that regulates their cellular location, protein stability, competency to bind steroid hormones and transcriptional activity (Echeverria and Picard, 2010). Ligand-binding to these receptors promotes dimerization and nuclear translocation. Other nuclear receptors are contstitutively nuclear and their chromatin-modifying activities are regulated by ligand binding (reviewed in Beato et al, 1996).

In addition to the classic transcriptional response, NRs also have a role in rapid, non-nuclear signaling originating from receptors localized at the plasma membrane. Ligand-binding to these receptors intitiates downstream phospholipase- and kinase-based signaling cascades (reviewed in Schwartz et al, 2016; Levin and Hammes, 2016).

Signaling by estrogen, liver X and retinoic acid receptors are currently described here.

Literature references

Hammes, SR., Levin, ER. (2016). Nuclear receptors outside the nucleus: extranuclear signalling by steroid receptors. *Nat. Rev. Mol. Cell Biol., 17*, 783-797. ↗

Edwards, DP., Simons, SS., Kumar, R. (2014). Minireview: dynamic structures of nuclear hormone receptors: new promises and challenges. *Mol. Endocrinol., 28*, 173-82. ↗

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Editions

2017-05-24	Authored, Edited	Rothfels, K.
2017-06-22	Reviewed	D'Eustachio, P.

6 submitted entities found in this pathway, mapping to 9 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BCL2	P10415	EGFR	P00533	KRAS	P01116-1, P01116-2
MAPK	P28482	Myc	P01106	PIK3CA	P42336

Input	Ensembl Id	Input	Ensembl Id
BCL2	ENSG00000171791	Myc	ENSG00000136997

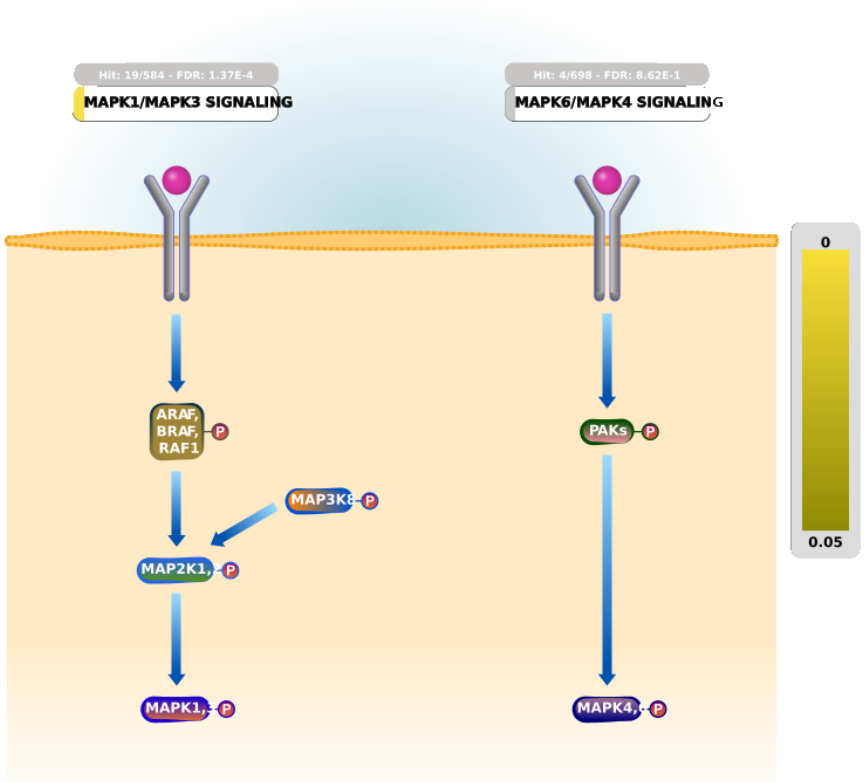
Interactors found in the analysis (15)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BAX	Q07812	P10415	BCL2	P10415	P10415
BRCA1	P38398	P24385, P52292	EGFR	P00533	Q05513, Q99075, P12931, P01135, Q05397, Q02790
IL10	P22301	P25490	IL2	IL2	Q13547
IL8	EBI-1566585	Q92793	JAK2	Q62120	P46527
MUC1	P15941	P12931	Myc	P01106, EBI-1265559	Q13547, P52292, P08047, O60341, O43524, O15169, P23771
NFKB1	P19838, P25799	Q15788, Q13547	PARP1	P09874	P22415
PIK3CA	P42336	P01100	STAT3	P40763	P08047, P12931, P06401
p53	P04637, P04637-7, P04637-1	Q09472, P17844, Q92793, P10415, Q13547, Q15648, O14980, P08047, O43524, O15169, Q05397			

MAPK family signaling cascades ↗

Location: Signal Transduction

Stable identifier: R-HSA-5683057



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

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

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

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

Literature references

Meloche, S., Coulombe, P. (2007). Atypical mitogen-activated protein kinases: structure, regulation and functions. *Biochim. Biophys. Acta, 1773*, 1376-87. ↗

Kyriakis, JM., Avruch, J. (2012). Mammalian MAPK signal transduction pathways activated by stress and inflammation: a 10-year update. *Physiol. Rev., 92*, 689-737. ↗

Zehorai, E., Procaccia, S., Seger, R., Plotnikov, A. (2011). The MAPK cascades: signaling components, nuclear roles and mechanisms of nuclear translocation. *Biochim. Biophys. Acta, 1813*, 1619-33. ↗

Roux, PP., Cargnello, M. (2011). Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol. Mol. Biol. Rev., 75*, 50-83. ↗

Editions

2015-03-10	Authored	Rothfels, K.
2015-04-29	Reviewed	Roskoski, R Jr.

12 submitted entities found in this pathway, mapping to 16 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BRAF	P15056	EGFR	P00533, P04626	IL2	P60568
IL5	P05113	IL6	P05231	JAK1	P23458
JAK2	O60674	JAK3	P52333	KRAS	P01116, P01116-1, P01116-2
MAPK	P28482	Myc	P01106	PIK3CA	P42336

Input	Ensembl Id
Myc	ENST00000377970

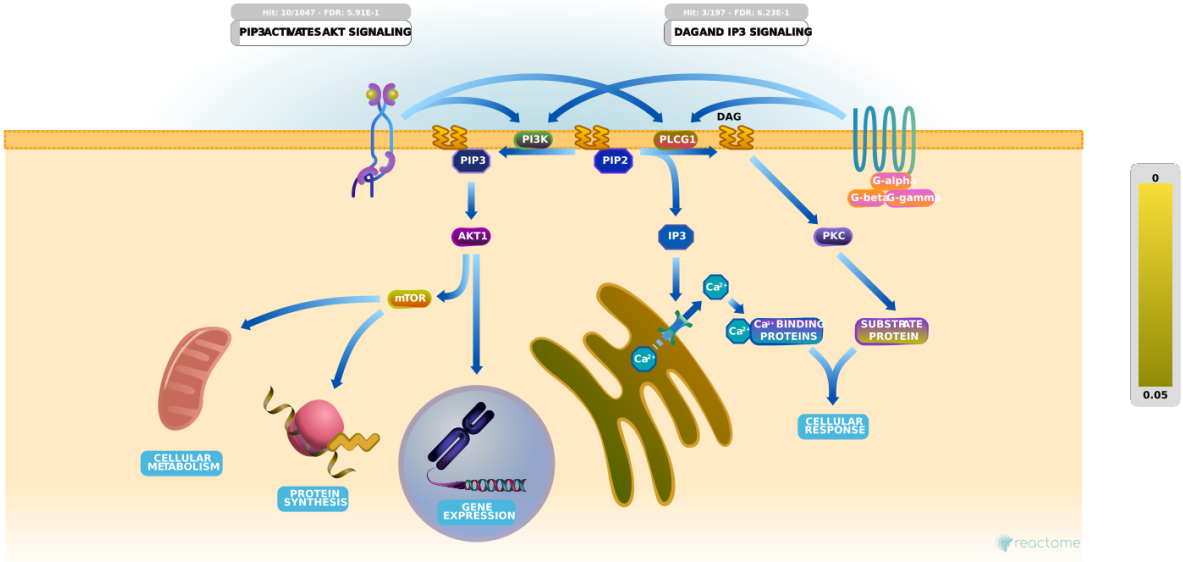
Interactors found in the analysis (8)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BAX	Q07812	Q07817	BCL2	P10415	P28482
BRAF	P15056	P04049, P36507, P15056, Q02750	BRCA1	P38398	Q7Z569
EGFR	P00533	P04049, P06493, P53041, P04792	KRAS	P01116-2, P01116, P32883	P04049, P15056, P01116-2
Myc	P01106	O43524, P04792	p53	P04637	P35232, O14980, O43524, P04792

Intracellular signaling by second messengers ↗

Location: Signal Transduction

Stable identifier: R-HSA-9006925



Second messengers are generated within the cell as a downstream step in signal transduction cascades initiated by the interaction of an external stimulus with a cell surface receptor. Common second messengers include DAG, cAMP, cGMP, IP3, Ca2+ and phosphatidylinositols (reviewed in Kang et al, 2015; Raker et al, 2016; Li and Marshall, 2015; Pinto et al, 2015; Ahmad et al, 2015).

Literature references

Kim, S., Kang, DS., Lee, C., Suh, PG., Yang, YR., Ryu, SH. (2016). Roles of phosphoinositide-specific phospholipase Cγ1 in brain development. *Adv Biol Regul, 60*, 167-73. ↗

Ulrich, H., Gomes, KN., Goulart, VA., Kihara, AH., Resende, RR., Pinto, MC. et al. (2015). Calcium signaling and cell proliferation. *Cell. Signal., 27*, 2139-49. ↗

Becker, C., Steinbrink, K., Raker, VK. (2016). The cAMP Pathway as Therapeutic Target in Autoimmune and Inflammatory Diseases. *Front Immunol, 7*, 123. ↗

Patel, S., Levine, TP. (2016). Signalling at membrane contact sites: two membranes come together to handle second messengers. *Curr. Opin. Cell Biol., 39*, 77-83. ↗

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Editions

2017-05-24	Authored, Edited	Rothfels, K.
2017-06-22	Reviewed	D'Eustachio, P.

4 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id
EGFR	P00533, P04626	MAPK	P28482
PIK3CA	P42336	p53	P04637

Interactors found in the analysis (8)

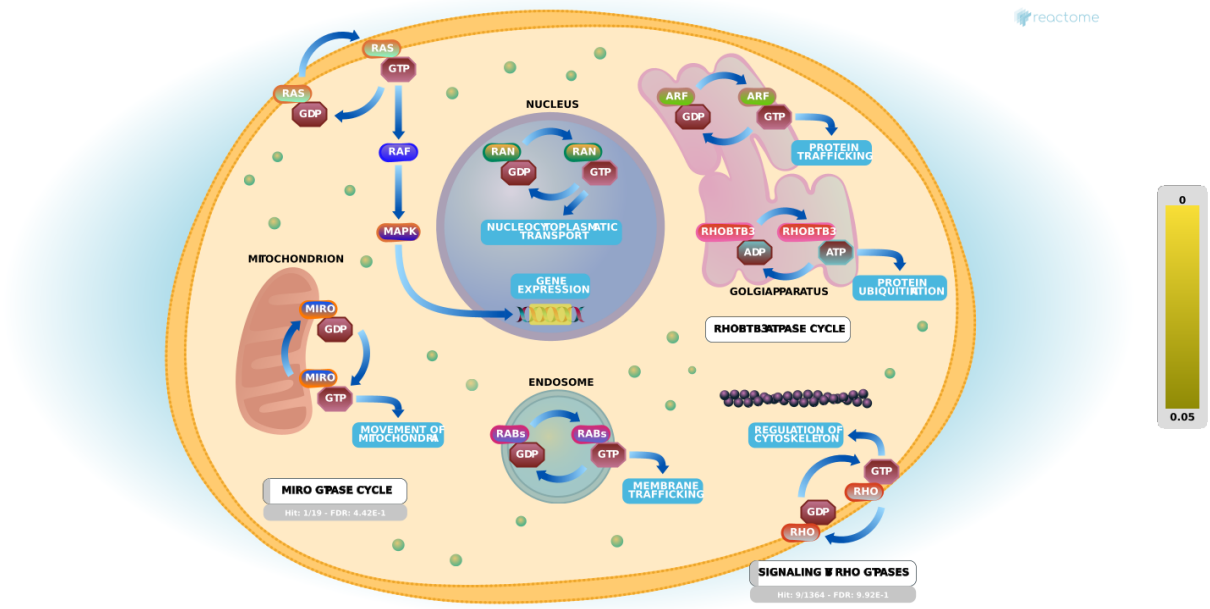
Input	UniProt Id	Interacts with
BCL2	P10415	P22736, Q92934
EGFR	P00533	P25098, P19174, P31749, P42685
NFKB1	P19838	O15111
STAT3	P40763	P22736

Input	UniProt Id	Interacts with
BRCA1	P38398	P52292
Myc	P01106	O15111, P52292
PARP1	P09874	Q9NTX7
p53	P04637	P22736, Q00987, P29590, Q9UHC7, Q93009

Signaling by Rho GTPases, Miro GTPases and RHOBTB3 ↗

Location: Signal Transduction

Stable identifier: R-HSA-9716542



RAS-like proteins are small GTP binding proteins characterized structurally by 5 G boxes that are involved in nucleotide binding and hydrolysis. RAS-like proteins are typically active when bound to GTP and inactive when bound to GDP. Conversion between the two states is mediated by effector proteins: among others, GTPase activating proteins (GAPs) enable hydrolysis of bound GTP to form GDP, which remains bound, and guanine nucleotide exchange factors (GEFs) enable exchange of bound GDP for free GTP (intracellular GTP concentrations are typically an order of magnitude higher than GDP concentrations) (reviewed in Tetlow and Tamanoi, 2013).

The human genome includes over 150 members of the RAS superfamily grouped into five main subfamilies: RAS, RHO, ARF, RAB and RAN. These small GTPases affect a wide range of critical processes including gene expression, signal transduction, cell morphology, vesicle and nuclear trafficking, cellular proliferation and motility, among others (reviewed in Tetlow and Tamanoi, 2013).

The RHO family of GTPases is large and diverse, with many of its members considered to be master regulators of actin cytoskeleton, involved in the regulation of cellular processes that depend on dynamic reorganization of the cytoskeleton, including cell migration, cell adhesion, cell division, establishment of cellular polarity and intracellular transport (reviewed in Hodge and Ridley 2016, and Olson 2018).

MIRO proteins and RHOBTB3 protein, sometimes called atypical RHO proteins, show a high degree of overall sequence similarity to members of the five RAS-like subfamilies but diverge in their functions enough to constitute two separate subfamilies (Boureux et al. 2007). MIRO proteins have intrinsically high GTPase activity and do not require GTPase activator proteins (Peters et al. 2018). They play an important role mitochondrial biogenesis, maintenance and organization (reviewed in Birsa et al. 2013). The GTPase domain of RHOBTB3 is divergent from other Ras like superfamily members and displays ATPase activity (Espinosa et al. 2009). RHOBTB3 is involved in CUL3 dependent protein ubiquitination (Berthold et al. 2008; Ji and Rivero 2016), retrograde transport from endosomes to the Golgi apparatus (Espinosa et al. 2009), regulation of the cell cycle and in modulating the adaptive response to hypoxia (Ji and Rivero 2016).

Literature references

Tamanoi, F., Tetlow, AL. (2013). The Ras superfamily G-proteins. *Enzymes, 33*, 1-14. ↗

Ji, W., Rivero, F. (2016). Atypical Rho GTPases of the RhoBTB Subfamily: Roles in Vesicle Trafficking and Tumorigenesis. *Cells, 5*. ↗

Schenkova, K., Berthold, J., Rivero, F. (2008). Rho GTPases of the RhoBTB subfamily and tumorigenesis. *Acta Pharmacol. Sin., 29*, 285-95. ↗

Norkett, R., Higgs, N., Lopez-Domenech, G., Birsa, N., Kittler, JT. (2013). Mitochondrial trafficking in neurons and the role of the Miro family of GTPase proteins. *Biochem. Soc. Trans., 41*, 1525-31. ↗

Olson, MF. (2018). Rho GTPases, their post-translational modifications, disease-associated mutations and pharmacological inhibitors. *Small GTPases, 9*, 203-215. ↗

Editions

2021-02-17	Authored	Rothfels, K.
2021-02-22	Edited	Orlic-Milacic, M.
2021-02-25	Reviewed	D'Eustachio, P.

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

Input	UniProt Id	Input	UniProt Id
MAPK	P28482	PIK3CA	P42336

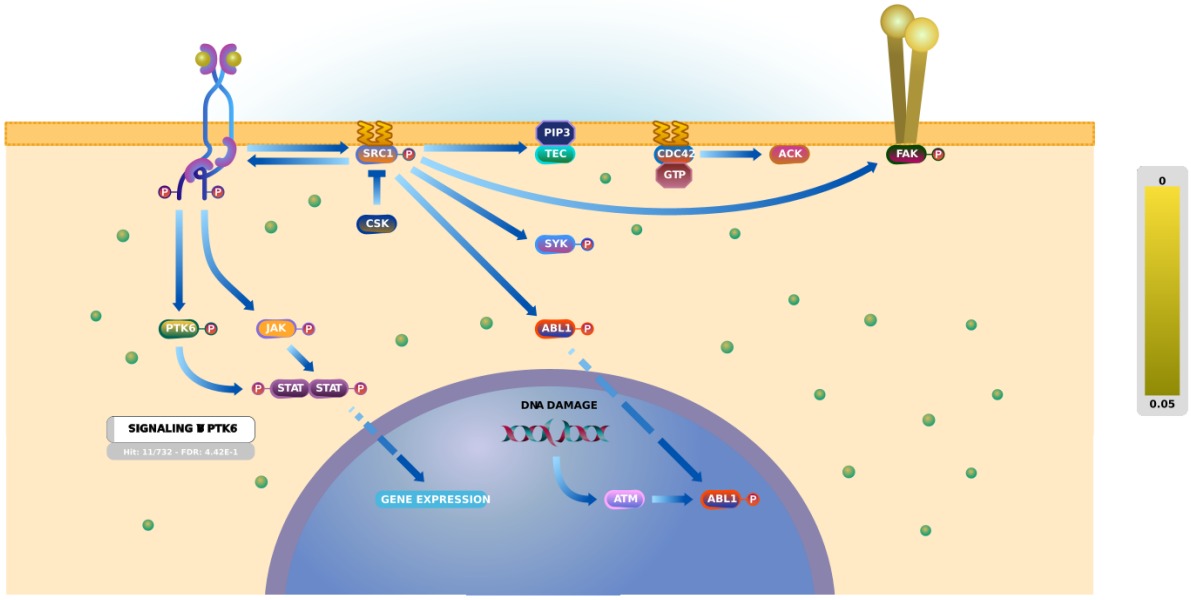
Interactors found in the analysis (7)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	Q14247, P00519, P30307, P23528, Q9UQB8, P52306, P12931, Q13153	JAK2	Q62120	P46527
MUC1	P15941	P00519, P12931	Myc	P01106	Q13526, O60341
NFKB1	P19838-PRO_0000030311	O00255	STAT3	P40763	P12931
p53	P04637	Q13526			

Signaling by Non-Receptor Tyrosine Kinases ↗

Location: Signal Transduction

Stable identifier: R-HSA-9006927



In addition to receptor tyrosine kinases, the human genome encodes at least 32 non-receptor tyrosine kinases (non-RTKs). These cytosolic tyrosine kinases lack a transmembrane domain but are recruited into signal transduction cascades through interaction with other plasma-bound receptors, which may or may not themselves have intrinsic catalytic activity. In this way, non-RTKs essentially function as an (additional) enzymatic subunit of the signaling complex and contribute to many of the same downstream signaling pathways. The non-RTKs can be grouped into 9 families (ABL, SYK, JAK, TEC, FAK, ACK, SRC, BRK/PTK6 and CSK) based on their domain structure (reviewed in Neet and Hunter, 1996).

Literature references

Neet, K., Hunter, T. (1996). Vertebrate non-receptor protein-tyrosine kinase families. *Genes Cells, 1*, 147-69. ↗

Editions

2017-05-24	Authored, Edited	Rothfels, K.
2017-06-22	Reviewed	D'Eustachio, P.

3 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
EGFR	P00533, P04626	KRAS	P01116-1, P01116-2	STAT3	P40763

Interactors found in the analysis (7)

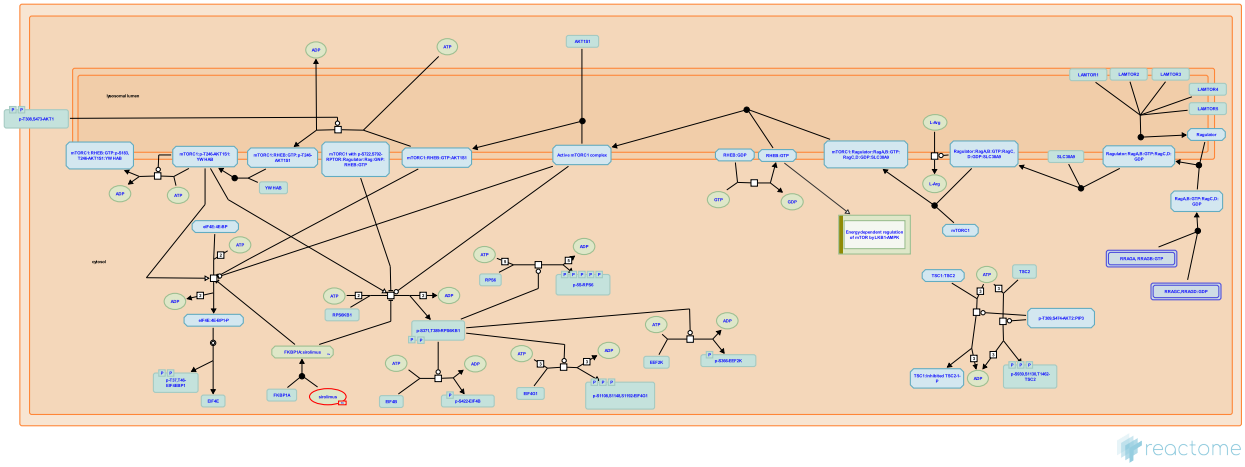
Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	Q9UGK3, P22681, Q14956, P31749, P18031, O14543, Q99704, P40763	JAK1	P23458	P40763
JAK2	O60674	P18031	Myc	EBI-1265559	P40763
NFKB1	P19838	Q8IZL8	STAT	EBI-10952519	P40763

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
STAT3	EBI-9914958, P40763	P22681, P18031, P40763			

MTOR signalling ↗

Location: Signal Transduction

Stable identifier: R-HSA-165159



Target of rapamycin (mTOR) is a highly-conserved serine/threonine kinase that regulates cell growth and division in response to energy levels, growth signals, and nutrients (Zoncu et al. 2011). Control of mTOR activity is critical for the cell since its dysregulation leads to cancer, metabolic disease, and diabetes (Laplante & Sabatini 2012). In cells, mTOR exists as two structurally distinct complexes termed mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), each one with specificity for different sets of effectors. mTORC1 couples energy and nutrient abundance to cell growth and proliferation by balancing anabolic (protein synthesis and nutrient storage) and catabolic (autophagy and utilization of energy stores) processes.

Literature references

Sabatini, DM., Zoncu, R., Efeyan, A. (2011). mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat. Rev. Mol. Cell Biol., 12*, 21-35. ↗

Editions

2015-01-23	Authored, Edited	Jupe, S.
2015-04-08	Revised	Jupe, S.
2015-05-14	Reviewed	Zwartkruis, FJ.

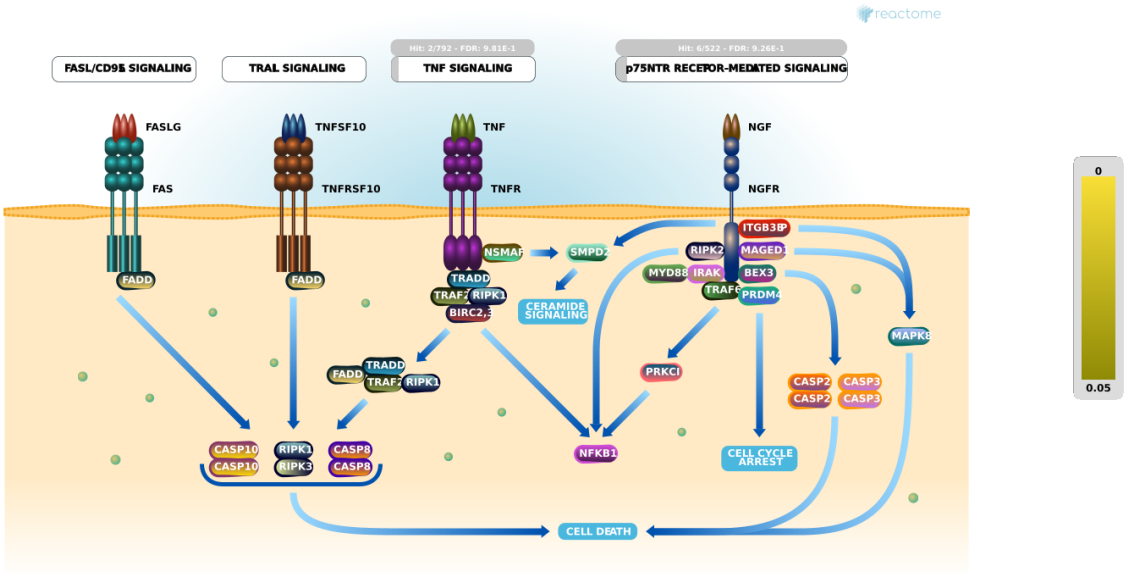
Interactors found in the analysis (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BRAF	P15056	P31946	EGFR	P00533	P35813, P31946, P31749

Death Receptor Signalling ↗

Location: Signal Transduction

Stable identifier: R-HSA-73887



The death receptors (DR), all cell-surface receptors, that belong to the TNF receptor superfamily (TNFRSF). The term death receptor refers to those members of the TNFRSF that contain a "death domain" (DD) within their cytoplasmic tail which provides the capacity for protein–protein interactions with other DD-containing proteins suach as FADD. The main signals transmitted from TNF death receptors such as TNFR1, TRAIL-R, and CD95/FAS in response to their cognate ligand binding result in an apoptotic signaling pathway characterized by direct activation of intracellular cysteine proteases (caspases), without directly involving the mitochondrial death pathway. However, these death receptors have also been shown to initiate survival signals via the activation of transcription factors NFκappaB and AP1. This project describes an assembly of the death-inducing signaling complex (DISC) downstream of TNFR1, TRAIL-R, and CD95/FAS and shows protein composition and stoichiometry within the DISC. However, the DISC signaling complex may vary in its components stoichiometry. DR signaling may trigger formation of higher order receptor structures or signaling through rearrangement of receptor chains, which is not reflected here. The project also describes neuron-type-specific signaling by the p75NTR death receptor (also known as NGFR) that can regulate a number of different biological activities in response to ligand binding, including cell death and/or survival, axonal growth and synaptic plasticity.

Editions

2004-08-10	Authored	Gillespie, ME.
2013-05-22	Reviewed	Salvesen, GS., Pop, C.
2022-05-18	Edited	Gillespie, ME.
2022-05-18	Reviewed	Vaux, DL.

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

Input	UniProt Id	Input	UniProt Id
NFKB1	P19838	TNF	P01375

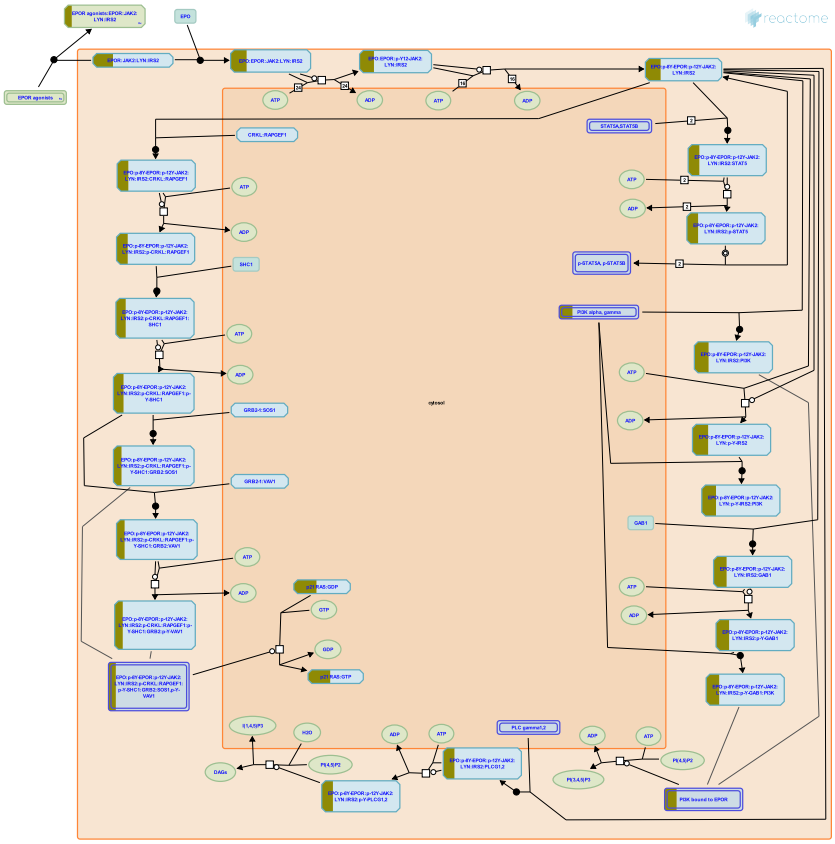
Interactors found in the analysis (5)

Input	UniProt Id	Interacts with
BAX	Q07812, Q07813-1	O43521
EGFR	P00533	Q12933, P45983
TNF	P01375	Q15628, Q12933, Q13546, P01375
BCL2	P10415	Q92934, O43521
NFKB1	P25799-1, P19838	P25963

Signaling by Erythropoietin ↗

Location: Signal Transduction

Stable identifier: R-HSA-9006335



Erythropoietin (EPO) is a cytokine that serves as the primary regulator of erythropoiesis, the differentiation of erythrocytes from stem cells in the liver of the fetus and the bone marrow of adult mammals (reviewed in Ingley 2012, Zhang et al. 2014, Kuhrt and Wojchowski 2015). EPO is produced in the kidneys in response to low oxygen tension and binds a receptor, EPOR, located on progenitor cells: burst forming unit-erythroid (BFU-e) cells and colony forming unit-erythroid (CFU-e) cells.

The erythropoietin receptor (EPOR) exists in lipid rafts (reviewed in McGraw and List 2017) as a dimer pre-associated with proteins involved in downstream signaling: the tyrosine kinase JAK2, the tyrosine kinase LYN, and the scaffold protein IRS2. Binding of EPO to the EPOR dimer causes a change in conformation (reviewed in Watowich et al. 2011, Corbett et al. 2016) that activates JAK2, which then transphosphorylates JAK2 and phosphorylates the cytoplasmic domain of EPOR. The phosphorylated EPOR serves directly or indirectly as a docking site for signaling molecules such as STAT5, phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K), phospholipase C gamma (PLCG1, PLCG2), and activators of RAS (SHC1, GRB2:SOS1, GRB2:VAV1).

EPO activates 4 major signaling pathways: STAT5-activated transcription, PI3K-AKT, RAS-RAF-ERK, and PLC-PKC. JAK2-STAT5 activates expression of BCL2L1 (Bcl-xL) and therefore appears to be important for anti-apoptosis. PI3K-AKT appears to be important for both anti-apoptosis and proliferation. The roles of other signaling pathways are controversial but both RAS-RAF-MEK-ERK and PLCgamma-PKC have mitogenic effects. Phosphatases such as SHP1 are also recruited and downregulate the EPO signal.

EPO also has effects outside of erythropoiesis. The EPOR is expressed in various tissues such as endothelium where it can act to stimulate growth and promote cell survival (Debeljak et al. 2014, Kimáková et al. 2017). EPO and EPOR in the neurovascular system act via Akt, Wnt1, mTOR, SIRT1, and FOXO proteins to

prevent apoptotic cell injury (reviewed in Ostrowski and Heinrich 2018, Maiese 2016) and EPO may have therapeutic value in the nervous system (Ma et al. 2016).

Literature references

Yue, W., Ma, C., Lian, Y., Cheng, F., Wang, Q., Wang, X. et al. (2016). Erythropoietin Pathway: A Potential Target for the Treatment of Depression. *Int J Mol Sci, 17*.

List, A., McGraw, K. (2017). Erythropoietin Receptor Signaling and Lipid Rafts. *Vitam. Horm., 105*, 79-100.

Zhang, Y., Alnaeeli, M., Dey, S., Wang, L., Suresh, S., Noguchi, CT. et al. (2014). Erythropoietin action in stress response, tissue maintenance and metabolism. *Int J Mol Sci, 15*, 10296-333.

Heinrich, R., Ostrowski, D. (2018). Alternative Erythropoietin Receptors in the Nervous System. *J Clin Med, 7*.

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

Editions

2017-04-22	Authored, Edited	May, B.
2018-08-14	Reviewed	McGraw, KL.

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

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
JAK2	O60674	KRAS	P01116-1, P01116-2	PIK3CA	P42336

Interactors found in the analysis (1)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	P29353, Q13480			

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