



Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 67 on 12/02/2019. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAxOTAyMTIxNDA5MTNfMTM4>

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
2. Properties
3. Genome-wide overview
4. Most significant pathways
5. Pathways details
6. Identifiers found
7. Identifiers not found

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:

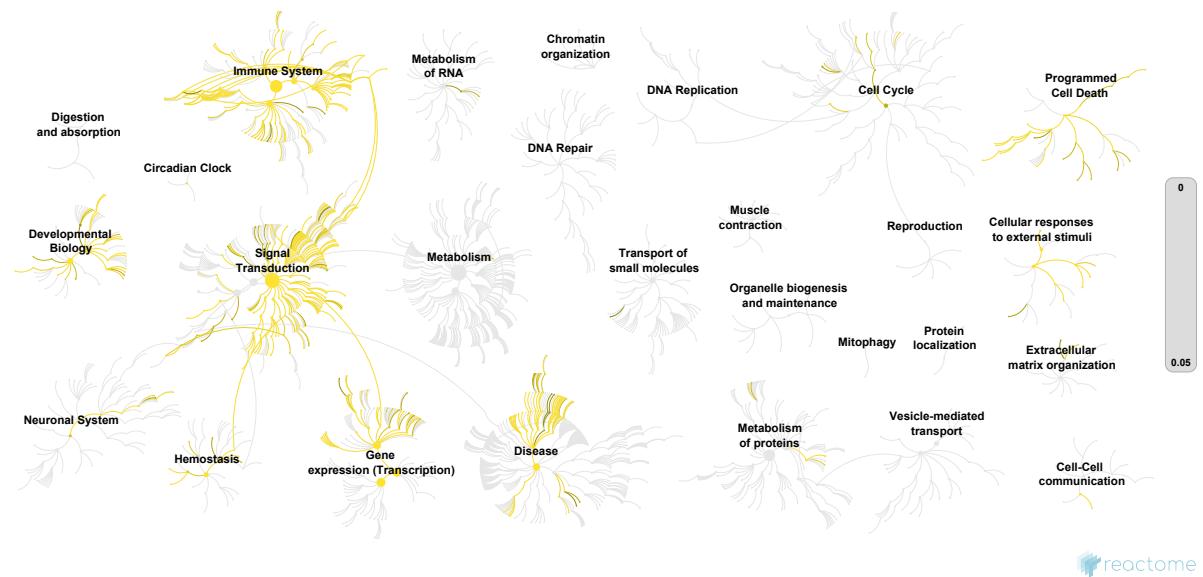
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, ... D'Eustachio P (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, 44(D1), D481–D487. <https://doi.org/10.1093/nar/gkv1351>.

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. ↗
- 190 out of 197 identifiers in the sample were found in Reactome, where 939 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. ↗
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAxOTAyMTIxNDA5MTNfMTM4. 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
Constitutive Signaling by AKT1 E17K in Cancer	19 / 32	0.002	1.11e-16	1.67e-15	18 / 18	0.002
PI3K/AKT Signaling in Cancer	47 / 133	0.009	1.11e-16	1.67e-15	21 / 21	0.002
Constitutive Signaling by Aberrant PI3K in Cancer	27 / 102	0.007	1.11e-16	1.67e-15	2 / 2	1.67e-04
TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	30 / 102	0.007	1.11e-16	1.67e-15	46 / 47	0.004
Signaling by SCF-KIT	20 / 50	0.004	1.11e-16	1.67e-15	35 / 36	0.003
MAP kinase activation	28 / 69	0.005	1.11e-16	1.67e-15	31 / 32	0.003
Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)	25 / 72	0.005	1.11e-16	1.67e-15	18 / 19	0.002
IGF1R signaling cascade	25 / 71	0.005	1.11e-16	1.67e-15	16 / 17	0.001
Signaling by FGFR in disease	23 / 93	0.007	1.11e-16	1.67e-15	99 / 106	0.009
Signaling by ERBB2	23 / 67	0.005	1.11e-16	1.67e-15	40 / 43	0.004
VEGFA-VEGFR2 Pathway	27 / 125	0.009	1.11e-16	1.67e-15	71 / 77	0.006
Insulin receptor signalling cascade	24 / 71	0.005	1.11e-16	1.67e-15	23 / 25	0.002
IRS-related events triggered by IGF1R	22 / 68	0.005	1.11e-16	1.67e-15	11 / 12	0.001
Signaling by VEGF	29 / 134	0.01	1.11e-16	1.67e-15	76 / 83	0.007
MyD88 cascade initiated on plasma membrane	30 / 94	0.007	1.11e-16	1.67e-15	51 / 57	0.005
IRS-mediated signalling	21 / 64	0.005	1.11e-16	1.67e-15	8 / 9	7.51e-04
Signaling by FGFR	23 / 106	0.008	1.11e-16	1.67e-15	126 / 142	0.012
TCF dependent signaling in response to WNT	32 / 216	0.015	1.11e-16	1.67e-15	63 / 71	0.006
Interleukin-17 signaling	28 / 77	0.005	1.11e-16	1.67e-15	31 / 35	0.003
Toll Like Receptor 5 (TLR5) Cascade	30 / 94	0.007	1.11e-16	1.67e-15	51 / 58	0.005
Toll Like Receptor 10 (TLR10) Cascade	30 / 94	0.007	1.11e-16	1.67e-15	51 / 58	0.005
MyD88 dependent cascade initiated on endosome	30 / 103	0.007	1.11e-16	1.67e-15	54 / 62	0.005
Toll Like Receptor 7/8 (TLR7/8) Cascade	30 / 103	0.007	1.11e-16	1.67e-15	54 / 63	0.005
MyD88:MAL(TIRAP) cascade initiated on plasma membrane	31 / 111	0.008	1.11e-16	1.67e-15	54 / 63	0.005

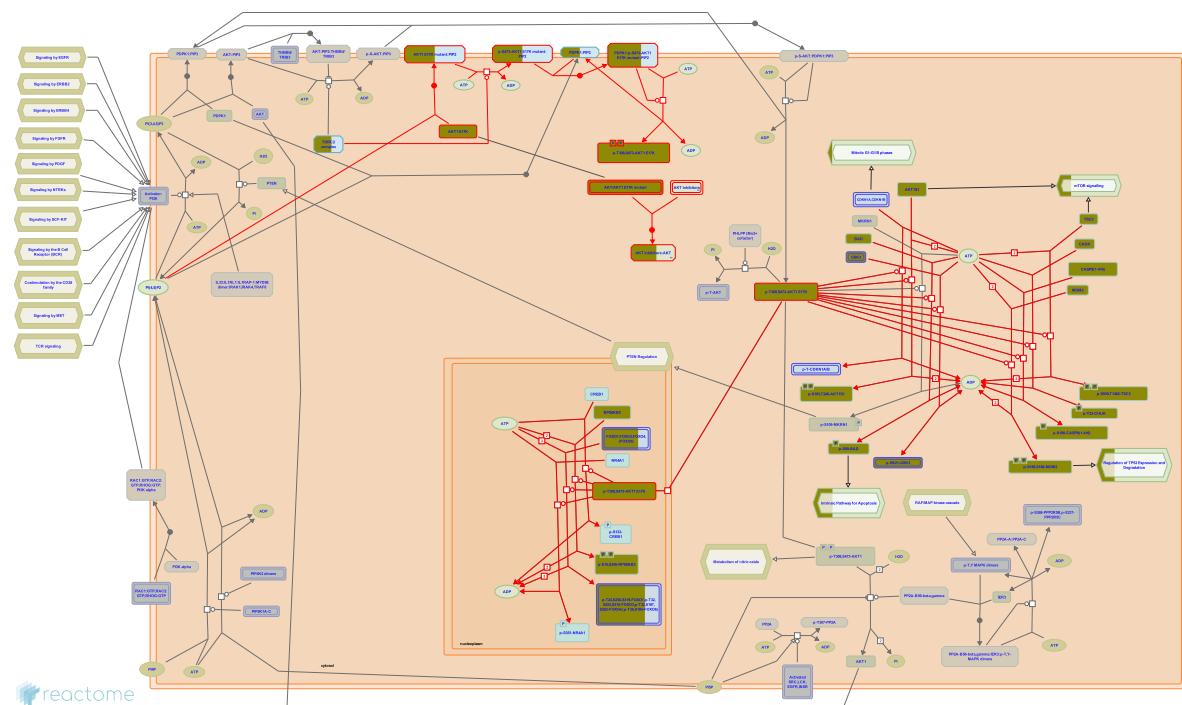
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
PIP3 activates AKT signaling	60 / 315	0.022	1.11e-16	1.67e-15	73 / 86	0.007

* 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. Constitutive Signaling by AKT1 E17K in Cancer (R-HSA-5674400)



Diseases: cancer.

While AKT1 gene copy number, expression level and phosphorylation are often increased in cancer, only one low frequency point mutation has been repeatedly reported in cancer and functionally studied. This mutation represents a substitution of a glutamic acid residue with lysine at position 17 of AKT1, and acts by enabling AKT1 to bind PIP2. PIP2-bound AKT1 is phosphorylated by TORC2 complex and by PDK1 that is always present at the plasma membrane, due to low affinity for PIP2. Therefore, E17K substitution abrogates the need for PI3K in AKT1 activation (Carpten et al. 2007, Landgraf et al. 2008).

References

- Carpten JD, Faber AL, Horn C, Donoho GP, Briggs SL, Robbins CM, ... Thomas JE (2007). A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. *Nature*, 448, 439-44. [🔗](#)
- Landgraf KE, Pilling C & Falke JJ (2008). Molecular mechanism of an oncogenic mutation that alters membrane targeting: Glu17Lys modifies the PIP lipid specificity of the AKT1 PH domain. *Biochemistry*, 47, 12260-9. [🔗](#)

Edit history

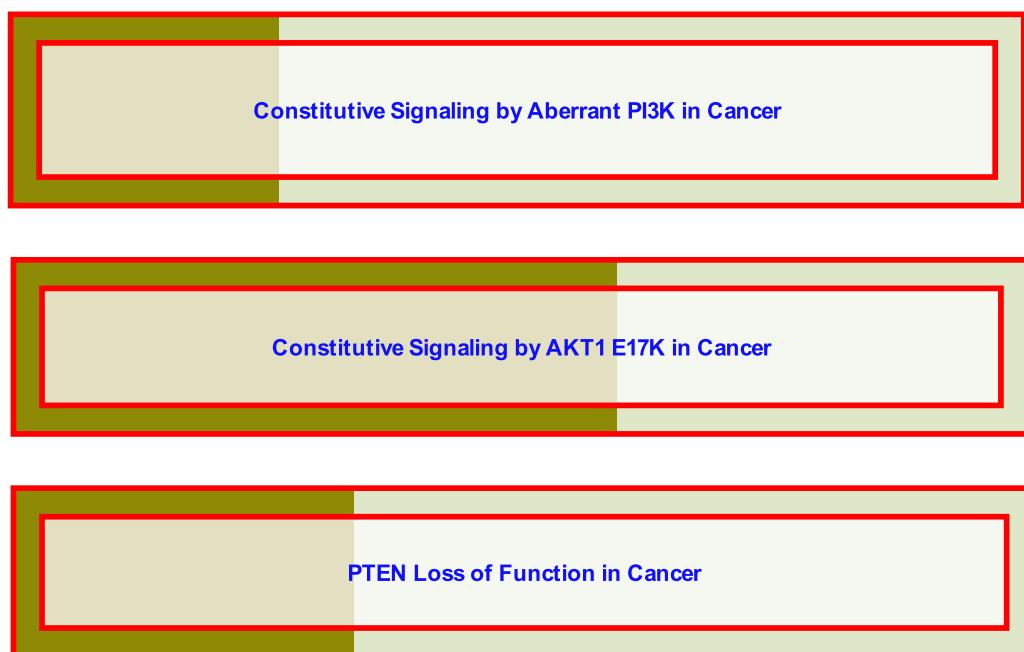
Date	Action	Author
2012-07-18	Authored	Orlic-Milacic M
2012-08-13	Reviewed	Yuzugullu H, Thorpe L, Zhao JJ

Date	Action	Author
2015-02-12	Created	Orlic-Milacic M
2018-12-05	Modified	Croft D

Entities found in this pathway (19)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31749, P31751, Q9Y243	AKT1S1	Q96B36	AKT2	P31751
AKT3	Q9Y243	BAD	Q92934	CASP9	P55211
CHUK	O15111	FOXO1	Q12778	FOXO3	O43524
FOXO4	P98177	GSK3A	P49840, P49841	GSK3B	P49841
MDM2	Q00987	MLST8	Q9BVC4	MTOR	P42345
PDPK1	O15530	RICTOR	Q6R327	RPS6KB2	Q9UBS0
TSC2	P49815				

2. PI3K/AKT Signaling in Cancer (R-HSA-2219528)



 reactome

Diseases: cancer.

Class IA PI3K is a heterodimer of a p85 regulatory subunit (encoded by PIK3R1, PIK3R2 or PIK3R3) and a p110 catalytic subunit (encoded by PIK3CA, PIK3CB or PIK3CD). In the absence of activating signals, the regulatory subunit stabilizes the catalytic subunit while inhibiting its activity. The complex becomes activated when extracellular signals stimulate the phosphorylation of the cytoplasmic domains of transmembrane receptors or receptor-associated proteins. The p85 regulatory subunit binds phosphorylated motifs of activator proteins, which induces a conformational change that relieves p85-mediated inhibition of the p110 catalytic subunit and enables PI3K to phosphorylate PIP2 to form PIP3. The phosphoinositide kinase activity of PI3K is opposed by the phosphoinositide phosphatase activity of PTEN.

PIP3 acts as a messenger that recruits PDPK1 (PDK1) and AKT (AKT1, AKT2 or AKT3) to the plasma membrane. PDPK1 also possesses a low affinity for PIP2, so small amounts of PDPK1 are always present at the membrane. Binding of AKT to PIP3 induces a conformational change that enables TORC2 complex to phosphorylate AKT at a conserved serine residue (S473 in AKT1). Phosphorylation at the serine residue enables AKT to bind to PDPK1 and exposes a conserved threonine residue (T308) that is phosphorylated by PDPK1. AKT phosphorylated at both serine and threonine residues dissociates from the plasma membrane and acts as a serine/threonine kinase that phosphorylates a number of cytosolic and nuclear targets involved in regulation of cell metabolism, survival and gene expression. For a recent review, please refer to Manning and Cantley, 2007.

Signaling by PI3K/AKT is frequently constitutively activated in cancer. This activation can be via gain-of-function mutations in PI3KCA (encoding catalytic subunit p110alpha), PIK3R1 (encoding regulatory subunit p85alpha) and AKT1. The PI3K/AKT pathway can also be constitutively activated by loss-of-function mutations in tumor suppressor genes such as PTEN.

Gain-of-function mutations activate PI3K signaling by diverse mechanisms. Mutations affecting the helical domain of PIK3CA and mutations affecting nSH2 and iSH2 domains of PIK3R1 impair inhibitory interactions between these two subunits while preserving their association. Mutations in the catalytic domain of PIK3CA enable the kinase to achieve an active conformation. PI3K complexes with gain-of-function mutations therefore produce PIP3 and activate downstream AKT in the absence of growth factors (Huang et al. 2007, Zhao et al. 2005, Miled et al. 2007, Horn et al. 2008, Sun et al. 2010, Jaiswal et al. 2009, Zhao and Vogt 2010, Urick et al. 2011). While AKT1 gene copy number, expression level and phosphorylation are often increased in cancer, only one low frequency point mutation has been repeatedly reported in cancer and functionally studied. This mutation represents a substitution of a glutamic acid residue with lysine at position 17 of AKT1, and acts by enabling AKT1 to bind PIP2. PIP2-bound AKT1 is phosphorylated by TORC2 complex and by PDPK1 that is always present at the plasma membrane, due to low affinity for PIP2. Therefore, E17K substitution abrogates the need for PI3K in AKT1 activation (Carpten et al. 2007, Landgraf et al. 2008).

Loss-of-function mutations affecting the phosphatase domain of PTEN are frequently found in sporadic cancers (Kong et al. 1997, Lee et al. 1999, Han et al. 2000), as well as in PTEN hamartoma tumor syndromes (PHTS) (Marsh et al. 1998). PTEN can also be inactivated by gene deletion or epigenetic silencing, or indirectly by overexpression of microRNAs that target PTEN mRNA (Huse et al. 2009). Cells with deficient PTEN function have increased levels of PIP3, and therefore increased AKT activity. For a recent review, please refer to Hollander et al. 2011.

Because of their clear involvement in human cancers, PI3K and AKT are targets of considerable interest in the development of small molecule inhibitors. Although none of the currently available inhibitors display preference for mutant variants of PIK3CA or AKT, several inhibitors targeting the wild-type kinases are undergoing clinical trials. These include dual PI3K/mTOR inhibitors, class I PI3K inhibitors, pan-PI3K inhibitors, and pan-AKT inhibitors. While none have yet been approved for clinical use, these agents show promise for future therapeutics. In addition, isoform-specific PI3K and AKT inhibitors are currently being developed, and may provide more specific treatments along with reduced side-effects. For a recent review, please refer to Liu et al. 2009.

References

- Manning BD & Cantley LC (2007). AKT/PKB signaling: navigating downstream. *Cell*, 129, 1261-74.
- Liu P, Cheng H, Roberts TM & Zhao JJ (2009). Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat Rev Drug Discov*, 8, 627-44.
- Hollander MC, Blumenthal GM & Dennis PA (2011). PTEN loss in the continuum of common cancers, rare syndromes and mouse models. *Nat. Rev. Cancer*, 11, 289-301.
- Huang CH, Mandelker D, Schmidt-Kittler O, Samuels Y, Velculescu VE, Kinzler KW, ... Amzel LM (2007). The structure of a human p110alpha/p85alpha complex elucidates the effects of oncogenic PI3Kalpha mutations. *Science*, 318, 1744-8.
- Zhao JJ, Liu Z, Wang L, Shin E, Loda MF & Roberts TM (2005). The oncogenic properties of mutant p110alpha and p110beta phosphatidylinositol 3-kinases in human mammary epithelial cells. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 18443-8.

Edit history

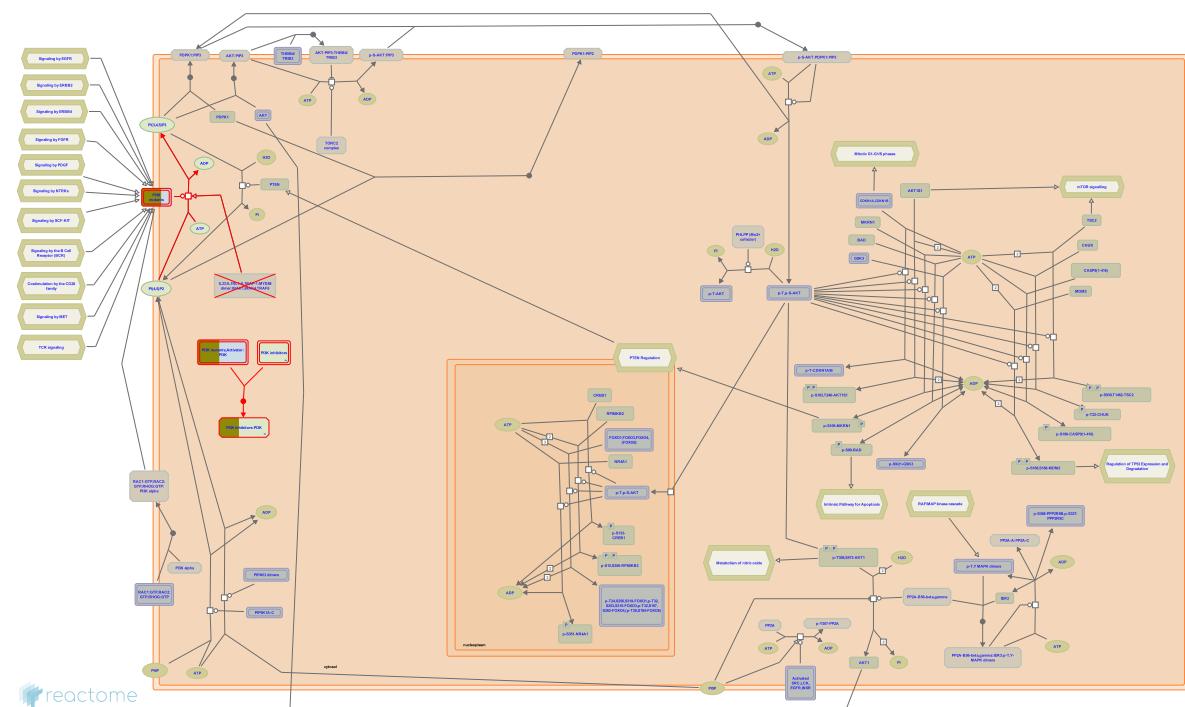
Date	Action	Author
2012-05-01	Created	Orlic-Milacic M

Date	Action	Author
2012-07-18	Authored	Orlic-Milacic M
2012-08-03	Edited	Matthews L
2012-08-13	Reviewed	Yuzugullu H, Thorpe L, Zhao JJ
2015-02-12	Modified	Orlic-Milacic M

Entities found in this pathway (41)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31749, P31751, Q9Y243	AKT1S1	Q96B36	AKT2	P31751
AKT3	Q9Y243	BAD	Q92934	CASP9	P55211
CHUK	O15111	EGFR	P00533	ERBB2	P04626
ERBB3	P21860-1	ERBB4	Q15303-1, Q15303-2	FGFR1	P11362-1, P11362-19
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5	FGFR3	P22607-1, P22607-2	FGFR4	P22455
FOXO1	Q12778	FOXO3	O43524	FOXO4	P98177
GAB1	Q13480	GRB2	P62993-1	GSK3A	P49840, P49841
GSK3B	P49841	IRS1	P35568	KIT	P10721
MDM2	Q00987	MET	P08581	MLST8	Q9BVC4
MTOR	P42345	PDGFRA	P16234	PDGFRB	P09619
PDPK1	O15530	PIK3CA	P42336	PTEN	P60484
PTPN11	Q06124	RAC1	P63000	RAC2	P15153
RICTOR	Q6R327	RPS6KB2	Q9UBS0	SRC	P12931
TSC2	P49815	VAV1	P15498		

3. Constitutive Signaling by Aberrant PI3K in Cancer (R-HSA-2219530)



Diseases: cancer.

Signaling by PI3K/AKT is frequently constitutively activated in cancer via gain-of-function mutations in one of the two PI3K subunits - PI3KCA (encoding the catalytic subunit p110alpha) or PIK3R1 (encoding the regulatory subunit p85alpha). Gain-of-function mutations activate PI3K signaling by diverse mechanisms. Mutations affecting the helical domain of PIK3CA and mutations affecting nSH2 and iSH2 domains of PIK3R1 impair inhibitory interactions between these two subunits while preserving their association. Mutations in the catalytic domain of PIK3CA enable the kinase to achieve an active conformation. PI3K complexes with gain-of-function mutations therefore produce PIP3 and activate downstream AKT in the absence of growth factors (Huang et al. 2007, Zhao et al. 2005, Miled et al. 2007, Horn et al. 2008, Sun et al. 2010, Jaiswal et al. 2009, Zhao and Vogt 2010, Urick et al. 2011).

References

- Huang CH, Mandelker D, Schmidt-Kittler O, Samuels Y, Velculescu VE, Kinzler KW, ... Amzel LM (2007). The structure of a human p110alpha/p85alpha complex elucidates the effects of oncogenic PI3Kalpha mutations. *Science*, 318, 1744-8. [🔗](#)
- Zhao JJ, Liu Z, Wang L, Shin E, Loda MF & Roberts TM (2005). The oncogenic properties of mutant p110alpha and p110beta phosphatidylinositol 3-kinases in human mammary epithelial cells. *Proc. Natl. Acad. Sci. U.S.A.*, 102, 18443-8. [🔗](#)
- Miled N, Yan Y, Hon WC, Perisic O, Zvelebil M, Inbar Y, ... Williams RL (2007). Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit. *Science*, 317, 239-42. [🔗](#)
- Horn S, Bergholz U, Jücker M, McCubrey JA, Trümper L, Stocking C & Bäsecke J (2008). Mutations in the catalytic subunit of class IA PI3K confer leukemogenic potential to hematopoietic cells. *Oncogene*, 27, 4096-106. [🔗](#)

Sun M, Hillmann P, Hofmann BT, Hart JR & Vogt PK (2010). Cancer-derived mutations in the regulatory subunit p85alpha of phosphoinositide 3-kinase function through the catalytic subunit p110alpha. Proc. Natl. Acad. Sci. U.S.A., 107, 15547-52. [🔗](#)

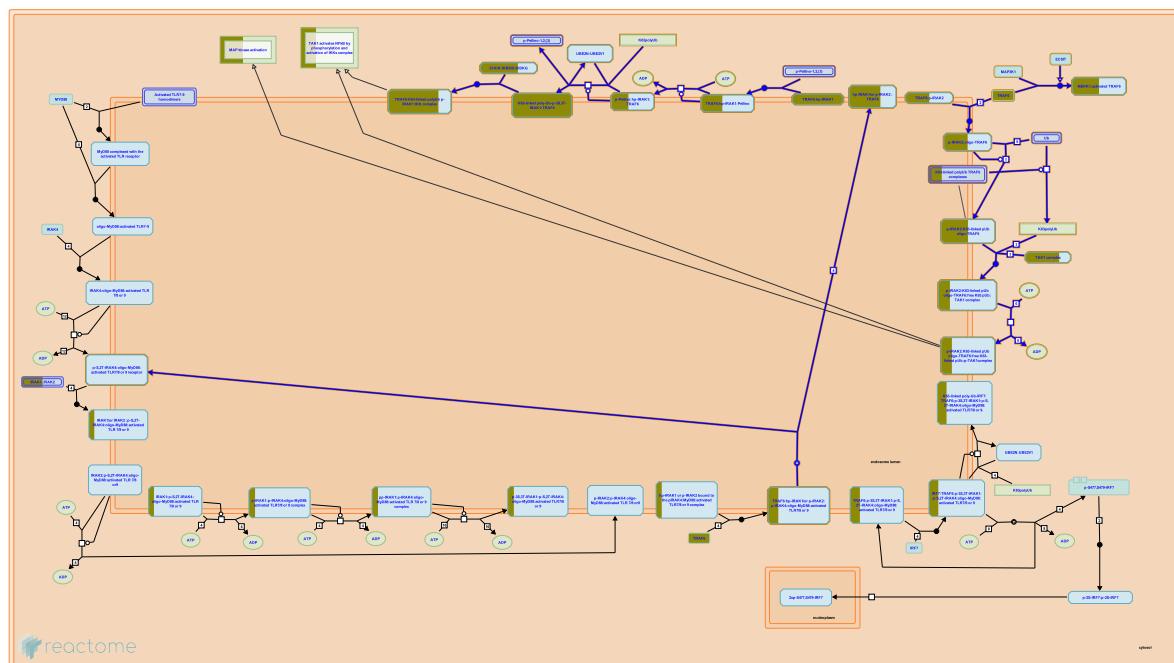
Edit history

Date	Action	Author
2012-05-01	Created	Orlic-Milacic M
2012-07-18	Authored	Orlic-Milacic M
2012-08-13	Reviewed	Yuzugullu H, Thorpe L, Zhao JJ
2018-12-05	Modified	Croft D

Entities found in this pathway (21)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
EGFR	P00533	ERBB2	P04626	ERBB3	P21860-1
ERBB4	Q15303-1, Q15303-2	FGFR1	P11362-1, P11362-19	FGFR2	P21802-1, P21802-18, P21802-3, P21802-5
FGFR3	P22607-1, P22607-2	FGFR4	P22455	GAB1	Q13480
GRB2	P62993-1	IRS1	P35568	KIT	P10721
MET	P08581	PDGFRA	P16234	PDGFRB	P09619
PIK3CA	P42336	PTPN11	Q06124	RAC1	P63000
RAC2	P15153	SRC	P12931	VAV1	P15498

4. TRAF6 mediated induction of NF κ B and MAP kinases upon TLR7/8 or 9 activation (R-HSA-975138)



Cellular compartments: cytosol, endosome membrane, nucleoplasm.

TRAF6 mediates NF κ B activation via canonical phosphorylation of IKK complex by TAK1. TRAF6 and TAK1 also regulate MAPK cascades leading to the activation of AP-1.

References

Pauls E, Shapiro N, Peggie M, Young ER, Sorcek RJ, Tan L, ... Cohen P (2012). Essential role for IKK? in production of type 1 interferons by plasmacytoid dendritic cells. *J. Biol. Chem.*, 287, 19216-28. [🔗](#)

Fraczek J, Kim TW, Xiao H, Yao J, Wen Q, Li Y, ... Li X (2008). The kinase activity of IL-1 receptor-associated kinase 4 is required for interleukin-1 receptor/toll-like receptor-induced TAK1-dependent NF κ B activation. *J. Biol. Chem.*, 283, 31697-705. [🔗](#)

Edit history

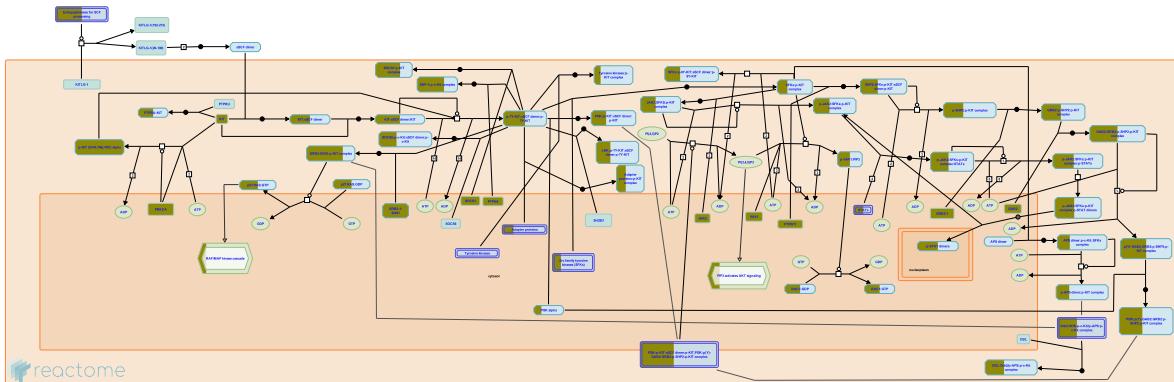
Date	Action	Author
2010-08-25	Authored	Shamovsky V
2010-09-22	Created	Shamovsky V
2010-10-29	Reviewed	Gillespie ME
2010-11-15	Edited	Shamovsky V
2018-12-05	Modified	Croft D

Entities found in this pathway (31)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATF2	P15336	BTRC	Q9Y297	CHUK	O15111
DUSP6	Q16828	FOS	P01100	IKBKB	O14920

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IRAK1	P51617	JUN	P05412	MAP2K1	Q02750
MAP2K3	P46734	MAP2K4	P45985	MAP2K7	O14733
MAP3K7	O43318	MAP3K8	P41279	MAPK1	P28482
MAPK14	Q16539	MAPK3	P27361	MAPK8	P45983
MAPK9	P45984	MAPKAPK2	P49137	NFKB1	P19838
NFKB2	Q00653	REL	Q00653	RELA	Q04206
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA5	O75582	TAB1	Q15750	TAB2	Q9NYJ8
TRAF6	Q9Y4K3				

5. Signaling by SCF-KIT (R-HSA-1433557)



Stem cell factor (SCF) is a growth factor with membrane bound and soluble forms. It is expressed by fibroblasts and endothelial cells throughout the body, promoting proliferation, migration, survival and differentiation of hematopoietic progenitors, melanocytes and germ cells.(Linnekin 1999, Ronnstrand 2004, Lennartsson and Ronnstrand 2006). The receptor for SCF is KIT, a tyrosine kinase receptor (RTK) closely related to the receptors for platelet derived growth factor receptor, colony stimulating factor 1 (Linnekin 1999) and Flt3 (Rosnet et al. 1991). Four isoforms of c-Kit have been identified in humans. Alternative splicing results in isoforms of KIT differing in the presence or absence of four residues (GNNK) in the extracellular region. This occurs due to the use of an alternate 5' splice donor site. These GNNK+ and GNNK- variants are co-expressed in most tissues; the GNNK-form predominates and was more strongly tyrosine-phosphorylated and more rapidly internalized (Ronnstrand 2004). There are also splice variants that arise from alternative usage of splice acceptor site resulting in the presence or absence of a serine residue (Crosier et al., 1993). Finally, there is an alternative shorter transcript of KIT expressed in postmeiotic germ cells in the testis which encodes a truncated KIT consisting only of the second part of the kinase domain and thus lacking the extracellular and transmembrane domains as well as the first part of the kinase domain (Rossi et al. 1991). Binding of SCF homodimers to KIT results in KIT homodimerization followed by activation of its intrinsic tyrosine kinase activity. KIT stimulation activates a wide array of signalling pathways including MAPK, PI3K and JAK/STAT (Reber et al. 2006, Ronnstrand 2004). Defects of KIT in humans are associated with different genetic diseases and also in several types of cancers like mast cell leukaemia, germ cell tumours, certain subtypes of malignant melanoma and gastrointestinal tumours.

References

- Edling CE & Hallberg B (2007). c-Kit--a hematopoietic cell essential receptor tyrosine kinase. *Int J Biochem Cell Biol*, 39, 1995-8. [🔗](#)
- Rönnstrand L (2004). Signal transduction via the stem cell factor receptor/c-Kit. *Cell Mol Life Sci*, 61, 2535-48. [🔗](#)
- Reber L, Da Silva CA & Frossard N (2006). Stem cell factor and its receptor c-Kit as targets for inflammatory diseases. *Eur J Pharmacol*, 533, 327-40. [🔗](#)
- Lennartsson J & Rönnstrand L (2006). The stem cell factor receptor/c-Kit as a drug target in cancer. *Curr Cancer Drug Targets*, 6, 65-75. [🔗](#)
- Masson K & Rönnstrand L (2009). Oncogenic signaling from the hematopoietic growth factor receptors c-Kit and Flt3. *Cell Signal*, 21, 1717-26. [🔗](#)

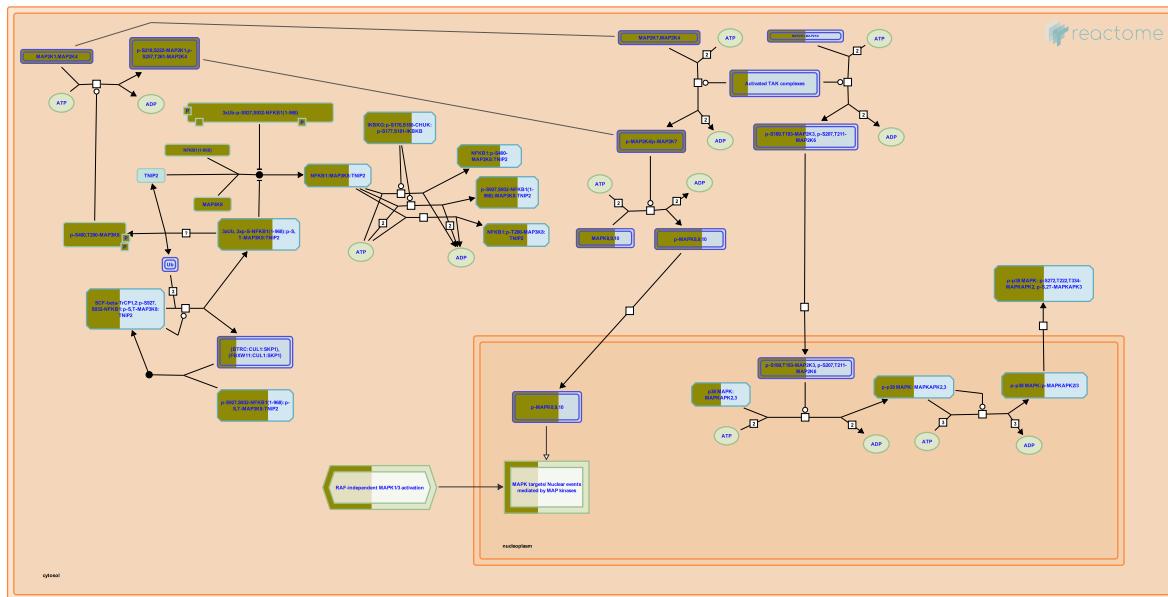
Edit history

Date	Action	Author
2011-07-11	Edited	Garapati P V
2011-07-11	Authored	Garapati P V
2011-07-11	Created	Garapati P V
2011-08-22	Reviewed	Rönnstrand L
2018-11-29	Modified	Weiser D

Entities found in this pathway (19)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
GAB2	Q9UQC2	GRAP2	O75791	GRB2	P62993-1
JAK2	O60674	KIT	P10721	KRAS	P01111, P01116
MMP9	P14780	PIK3CA	P42336	PRKACA	P17252
PRKCA	P17252	PTPN11	Q06124	PTPN6	P29350
RAC1	P63000	SOCS1	O15524	SOS1	Q07889
SRC	P12931-1	STAT1	P42224, P42224-1	STAT3	P40763
VAV1	P15498				

6. MAP kinase activation (R-HSA-450294)



Cellular compartments: cytosol, nucleoplasm.

The mitogen activated protein kinase (MAPK) cascade, one of the most ancient and evolutionarily conserved signaling pathways, is involved in many processes of immune responses. The MAP kinases cascade transduces signals from the cell membrane to the nucleus in response to a wide range of stimuli (Chang and Karin, 2001; Johnson et al, 2002).

There are three major groups of MAP kinases

- the extracellular signal-regulated protein kinases ERK1/2,
- the p38 MAP kinase
- and the c-Jun NH-terminal kinases JNK.

ERK1 and ERK2 are activated in response to growth stimuli. Both JNKs and p38-MAPK are activated in response to a variety of cellular and environmental stresses. The MAP kinases are activated by dual phosphorylation of Thr and Tyr within the tripeptide motif Thr-Xaa-Tyr. The sequence of this tripeptide motif is different in each group of MAP kinases: ERK (Thr-Glu-Tyr); p38 (Thr-Gly-Tyr); and JNK (Thr-Pro-Tyr).

MAPK activation is mediated by signal transduction in the conserved three-tiered kinase cascade: MAPKKKK (MAP4K or MKKKK or MAPKKK Kinase) activates the MAPKK. The MAPKKKs then phosphorylates a dual-specificity protein kinase MAPKK, which in turn phosphorylates the MAPK.

The dual specificity MAP kinase kinases (MAPKK or MKK) differ for each group of MAPK. The ERK MAP kinases are activated by the MKK1 and MKK2; the p38 MAP kinases are activated by MKK3, MKK4, and MKK6; and the JNK pathway is activated by MKK4 and MKK7. The ability of MAP kinase kinases (MKKs, or MEKs) to recognize their cognate MAPKs is facilitated by a short docking motif (the D-site) in the MKK N-terminus, which binds to a complementary region on the MAPK. MAPKs then recognize many of their targets using the same strategy, because many MAPK substrates also contain D-sites.

The upstream signaling events in the TLR cascade that initiate and mediate the ERK signaling pathway remain unclear.

References

Chang L & Karin M (2001). Mammalian MAP kinase signalling cascades. Nature, 410, 37-40. [View](#)

Dong C, Davis RJ & Flavell RA (2002). MAP kinases in the immune response. *Annu Rev Immunol*, 20, 55-72. [\[C\]](#)

Banerjee A & Gerondakis S (2007). Coordinating TLR-activated signaling pathways in cells of the immune system. *Immunol Cell Biol*, 85, 420-4. [\[C\]](#)

Bardwell AJ, Frankson E & Bardwell L (2009). Selectivity of docking sites in MAPK kinases. *J Biol Chem*, 284, 13165-73. [\[C\]](#)

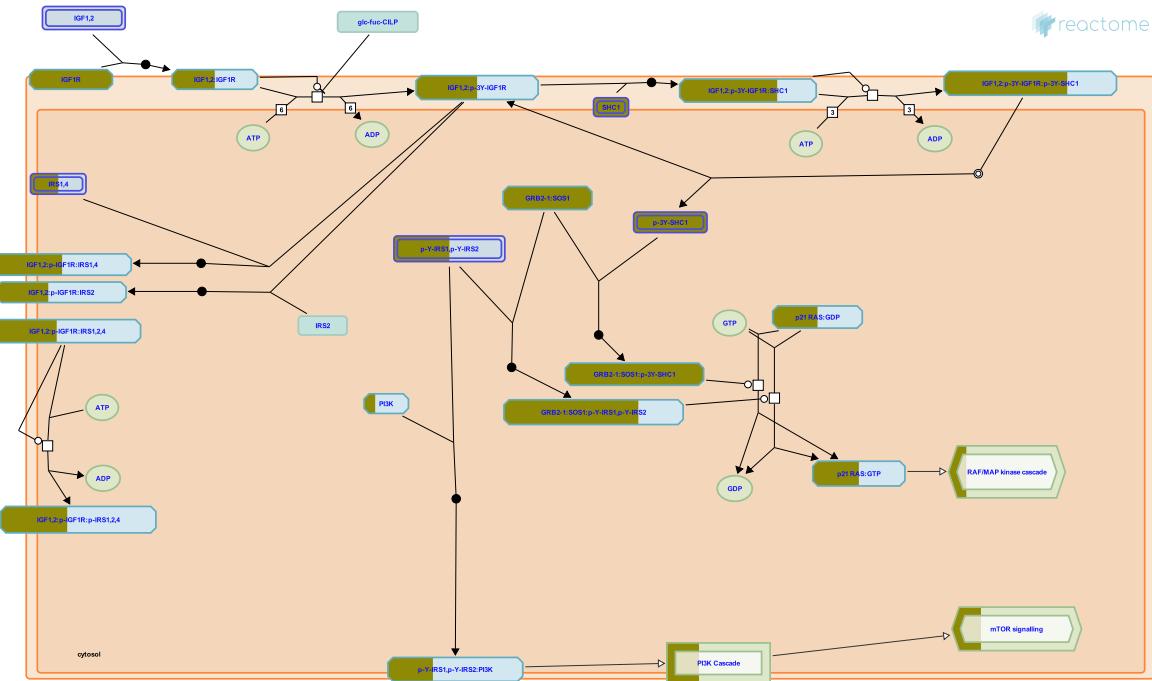
Edit history

Date	Action	Author
2009-12-16	Authored	Shamovsky V
2009-12-16	Created	Shamovsky V
2010-02-28	Edited	Shamovsky V
2010-02-28	Reviewed	Gillespie ME
2018-11-29	Modified	Weiser D

Entities found in this pathway (28)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATF2	P15336	BTRC	Q9Y297	CHUK	O15111
DUSP6	Q16828	FOS	P01100	IKBKB	O14920
IRAK1	P51617	JUN	P05412	MAP2K1	Q02750
MAP2K3	P46734	MAP2K4	P45985	MAP2K7	O14733
MAP3K7	O43318	MAP3K8	P41279	MAPK1	P28482
MAPK14	Q16539	MAPK3	P27361	MAPK8	P45983
MAPK9	P45984	MAPKAPK2	P49137	NFKB1	P19838
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA5	O75582	TAB1	Q15750	TAB2	Q9NYJ8
TRAF6	Q9Y4K3				

7. Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R) (R-HSA-2404192)



Cellular compartments: plasma membrane, cytosol, extracellular region.

Binding of IGF1 (IGF-I) or IGF2 (IGF-II) to the extracellular alpha peptides of the type 1 insulin-like growth factor receptor (IGF1R) triggers the activation of two major signaling pathways: the SOS-RAS-RAF-MAPK (ERK) pathway and the PI3K-PKB (AKT) pathway (recently reviewed in Pavelic et al. 2007, Chitnis et al. 2008, Maki et al. 2010, Parella et al. 2010, Annunziata et al. 2011, Siddle et al. 2012, Holzenberger 2012).

References

- Siddle K (2012). Molecular basis of signaling specificity of insulin and IGF receptors: neglected corners and recent advances. *Front Endocrinol (Lausanne)*, 3, 34. [🔗](#)
- Annunziata M, Granata R & Ghigo E (2011). The IGF system. *Acta Diabetol*, 48, 1-9. [🔗](#)
- Maki RG (2010). Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer. *J. Clin. Oncol.*, 28, 4985-95. [🔗](#)
- Chitnis MM, Yuen JS, Protheroe AS, Pollak M & Macaulay VM (2008). The type 1 insulin-like growth factor receptor pathway. *Clin. Cancer Res.*, 14, 6364-70. [🔗](#)
- Parrella E & Longo VD (2010). Insulin/IGF-I and related signaling pathways regulate aging in nondividing cells: from yeast to the mammalian brain. *ScientificWorldJournal*, 10, 161-77. [🔗](#)

Edit history

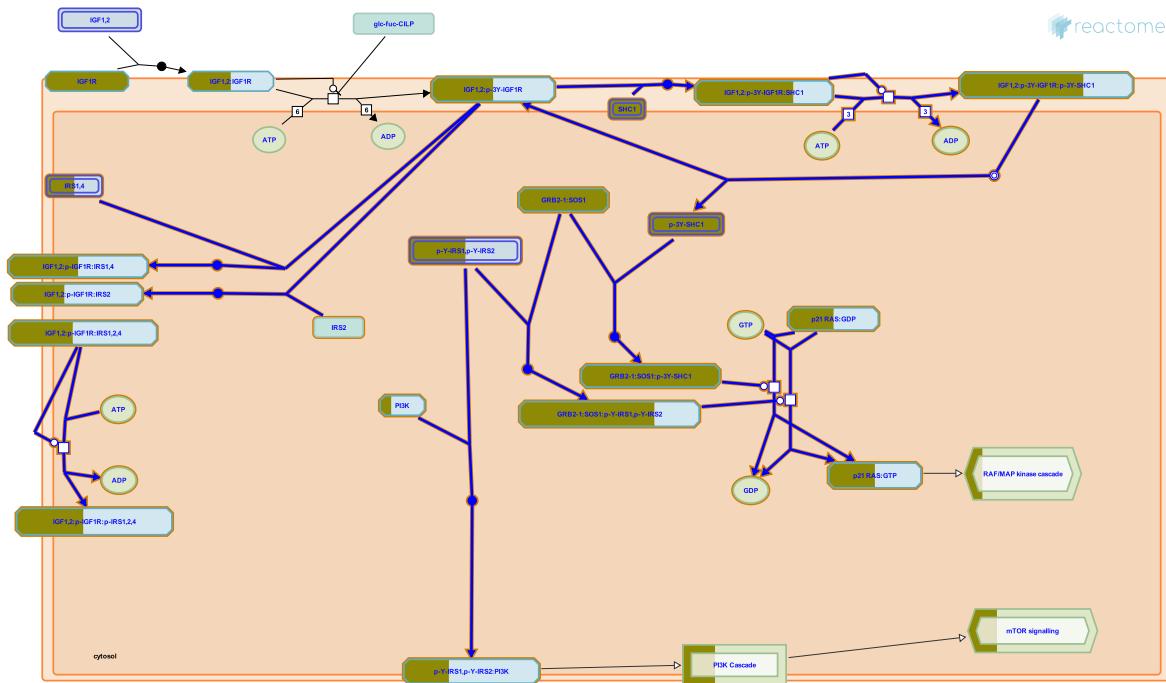
Date	Action	Author
2012-07-08	Edited	May B
2012-07-08	Authored	May B
2012-07-16	Created	May B

Date	Action	Author
2012-11-10	Reviewed	Holzenberger M
2018-12-05	Modified	Croft D

Entities found in this pathway (18)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31751	AKT2	P31751	FGFR1	P11362-1, P11362-19
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5	FGFR3	P22607-1, P22607-2	FGFR4	P22455
FLT3	P36888	GAB1	Q13480	GAB2	Q9UQC2
GRB2	P62993-1	IGF1R	P08069	IRS1	P35568
KRAS	P01111, P01116	PDPK1	O15530	PIK3CA	P42336
PTPN11	Q06124	SHC1	P29353-1, P29353-2, P29353-3	SOS1	Q07889

8. IGF1R signaling cascade (R-HSA-2428924)



Cellular compartments: cytosol, plasma membrane.

After autophosphorylation the type 1 insulin-like growth factor receptor (IGF1R) binds and phosphorylates scaffold proteins, IRS1/2/4 and SHC1, which in turn bind effectors possessing enzymatic activity (recently reviewed in Pavelic et al. 2007, Chitnis et al. 2008, Maki et al. 2010, Parrella et al. 2010, and Siddle et al. 2012). IRS1/2/4 can bind both PI3K (via the p85 subunit of PI3K) and the GRB2:SOS complex. PI3K activates PKB (AKT, AKT1) signaling. GRB:SOS stimulates RAS to exchange GDP for GTP leading to activation of RAF and MAPK.

References

- Paveli J, Matijevi T & Knezevi J (2007). Biological & physiological aspects of action of insulin-like growth factor peptide family. Indian J. Med. Res., 125, 511-22. [🔗](#)
- Parrella E & Longo VD (2010). Insulin/IGF-I and related signaling pathways regulate aging in nondividing cells: from yeast to the mammalian brain. ScientificWorldJournal, 10, 161-77. [🔗](#)
- Siddle K (2012). Molecular basis of signaling specificity of insulin and IGF receptors: neglected corners and recent advances. Front Endocrinol (Lausanne), 3, 34. [🔗](#)
- Maki RG (2010). Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer. J. Clin. Oncol., 28, 4985-95. [🔗](#)
- Annunziata M, Granata R & Ghigo E (2011). The IGF system. Acta Diabetol, 48, 1-9. [🔗](#)

Edit history

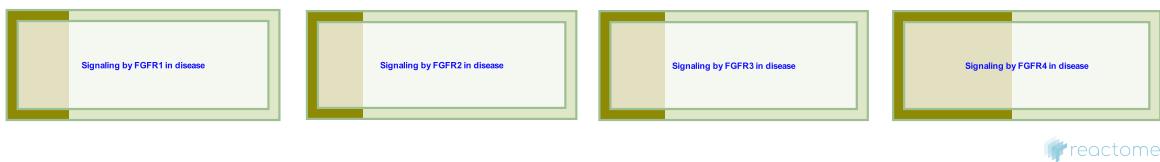
Date	Action	Author
2012-08-07	Edited	May B
2012-08-07	Authored	May B
2012-08-09	Created	May B

Date	Action	Author
2012-11-10	Reviewed	Holzenberger M
2018-11-29	Modified	Weiser D

Entities found in this pathway (18)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31751	AKT2	P31751	FGFR1	P11362-1, P11362-19
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5	FGFR3	P22607-1, P22607-2	FGFR4	P22455
FLT3	P36888	GAB1	Q13480	GAB2	Q9UQC2
GRB2	P62993-1	IGF1R	P08069	IRS1	P35568
KRAS	P01111, P01116	PDPK1	O15530	PIK3CA	P42336
PTPN11	Q06124	SHC1	P29353-1, P29353-2, P29353-3	SOS1	Q07889

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



Diseases: bone development disease, cancer.

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

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

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

References

- Webster MK & Donoghue DJ (1997). FGFR activation in skeletal disorders: too much of a good thing. Trends Genet, 13, 178-82. [🔗](#)
- Burke D, Wilkes D, Blundell TL & Malcolm S (1998). Fibroblast growth factor receptors: lessons from the genes. Trends Biochem Sci, 23, 59-62. [🔗](#)
- Cunningham ML, Seto ML, Ratisoontorn C, Heike CL & Hing AV (2007). Syndromic craniosynostosis: from history to hydrogen bonds. Orthod Craniofac Res, 10, 67-81. [🔗](#)
- Harada D, Yamanaka Y, Ueda K, Tanaka H & Seino Y (2009). FGFR3-related dwarfism and cell signaling. J Bone Miner Metab, 27, 9-15. [🔗](#)
- Galvin BD, Hart KC, Meyer AN, Webster MK & Donoghue DJ (1996). Constitutive receptor activation by Crouzon syndrome mutations in fibroblast growth factor receptor (FGFR)2 and FGFR2/Neu chimeras. Proc Natl Acad Sci U S A, 93, 7894-9. [🔗](#)

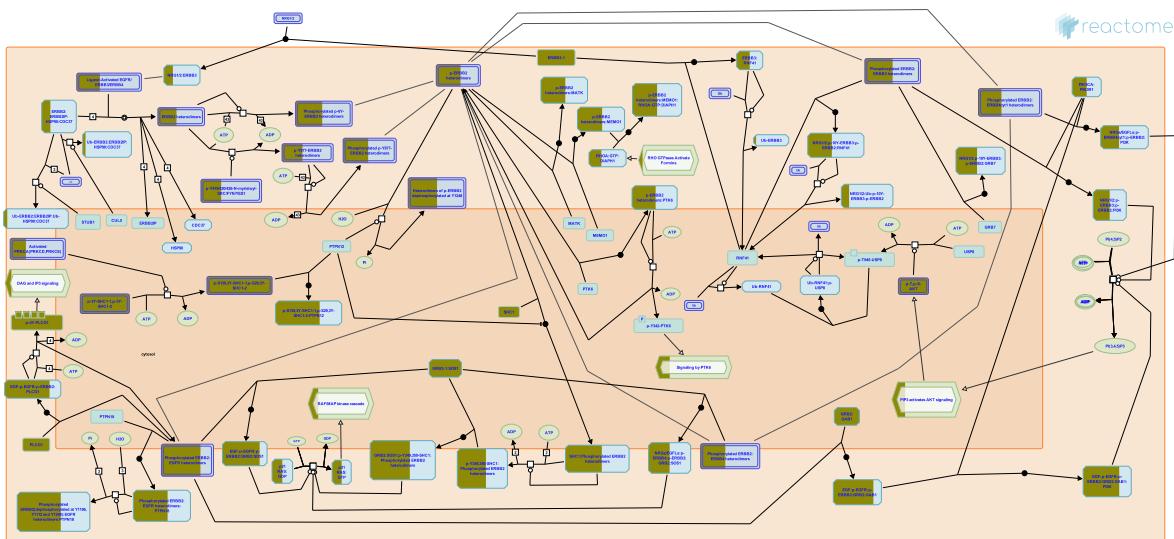
Edit history

Date	Action	Author
2011-03-09	Created	Rothfels K
2012-02-10	Authored	Rothfels K
2012-05-15	Edited	Rothfels K
2012-05-15	Reviewed	Ezzat S
2016-01-25	Reviewed	Grose RP
2016-09-16	Modified	Weiser JD

Entities found in this pathway (13)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
FGFR1	P11362, P11362-1, P11362-19	FGFR2	P21802, P21802-1, P21802-17, P21802-18, P21802-3, P21802-5	FGFR3	P22607, P22607-1, P22607-2
FGFR4	P22455	GAB1	Q13480	GAB2	Q9UQC2
GRB2	P62993-1	KRAS	P01111, P01116	PIK3CA	P42336
PLCG1	P19174	SOS1	Q07889	STAT1	P42224
STAT3	P40763				

10. Signaling by ERBB2 (R-HSA-1227986)



Cellular compartments: cytosol, plasma membrane, extracellular region.

ERBB2, also known as HER2 or NEU, is a receptor tyrosine kinase (RTK) belonging to the EGFR family. ERBB2 possesses an extracellular domain that does not bind any known ligand, contrary to other EGFR family members, a single transmembrane domain, and an intracellular domain consisting of an active kinase and a C-tail with multiple tyrosine phosphorylation sites. Inactive ERBB2 is associated with a chaperone heat shock protein 90 (HSP90) and its co-chaperone CDC37 (Xu et al. 2001, Citri et al. 2004, Xu et al. 2005). In addition, ERBB2 is associated with ERBB2IP (also known as ERBIN or LAP2), a protein responsible for proper localization of ERBB2. In epithelial cells, ERBB2IP restricts expression of ERBB2 to basolateral plasma membrane regions (Borg et al. 2000).

ERBB2 becomes activated by forming a heterodimer with another ligand-activated EGFR family member, either EGFR, ERBB3 or ERBB4, which is accompanied by dissociation of chaperoning proteins HSP90 and CDC37 (Citri et al. 2004), as well as ERBB2IP (Borg et al. 2000) from ERBB2. ERBB2 heterodimers function to promote cell proliferation, cell survival and differentiation, depending on the cellular context. ERBB2 can also be activated by homodimerization when it is overexpressed, in cancer for example.

In cells expressing both ERBB2 and EGFR, EGF stimulation of EGFR leads to formation of both ERBB2:EGFR heterodimers (Wada et al. 1990, Karunagaran et al. 1996) and EGFR homodimers. Heterodimers of ERBB2 and EGFR trans-autophosphorylate on twelve tyrosine residues, six in the C-tail of EGFR and six in the C-tail of ERBB2 - Y1023, Y1139, Y1196, Y1221, Y1222 and Y1248 (Margolis et al. 1989, Hazan et al. 1990, Walton et al. 1990, Helin et al. 1991, Ricci et al. 1995, Pinkas-Kramarski 1996). Phosphorylated tyrosine residues in the C-tail of EGFR and ERBB2 serve as docking sites for downstream signaling molecules. Three key signaling pathways activated by ERBB2:EGFR heterodimers are RAF/MAP kinase cascade, PI3K-induced AKT signaling, and signaling by phospholipase C gamma (PLCG1). Downregulation of EGFR signaling is mediated by ubiquitin ligase CBL, and is shown under Signaling by EGFR.

In cells expressing ERBB2 and ERBB3, ERBB3 activated by neuregulin NRG1 or NRG2 binding (Tzahar et al. 1994) forms a heterodimer with ERBB2 (Pinkas-Kramarski et al. 1996, Citri et al. 2004). ERBB3 is the only EGFR family member with no kinase activity, and can only function in heterodimers, with ERBB2 being its preferred heterodimerization partner. After heterodimerization, ERBB2 phosphorylates ten tyrosine residues in the C-tail of ERBB3, Y1054, Y1197, Y1199, Y1222, Y1224, Y1260, Y1262, Y1276, Y1289 and Y1328 (Prigent et al. 1994, Pinkas-Kramarski et al. 1996, Vijapurkar et al. 2003, Li et al. 2007) that subsequently serve as docking sites for downstream signaling molecules, resulting in activation of PI3K-induced AKT signaling and RAF/MAP kinase cascade. Signaling by ERBB3 is downregulated by the action of RNF41 ubiquitin ligase, also known as NRDPI.

In cells expressing ERBB2 and ERBB4, ligand stimulated ERBB4 can either homodimerize or form heterodimers with ERBB2 (Li et al. 2007), resulting in trans-autophosphorylation of ERBB2 and ERBB4 on C-tail tyrosine residues that will subsequently serve as docking sites for downstream signaling molecules, leading to activation of RAF/MAP kinase cascade and, in the case of ERBB4 CYT1 isoforms, PI3K-induced AKT signaling (Hazan et al. 1990, Cohen et al. 1996, Li et al. 2007, Kaushansky et al. 2008). Signaling by ERBB4 is downregulated by the action of WWP1 and ITCH ubiquitin ligases, and is shown under Signaling by ERBB4.

References

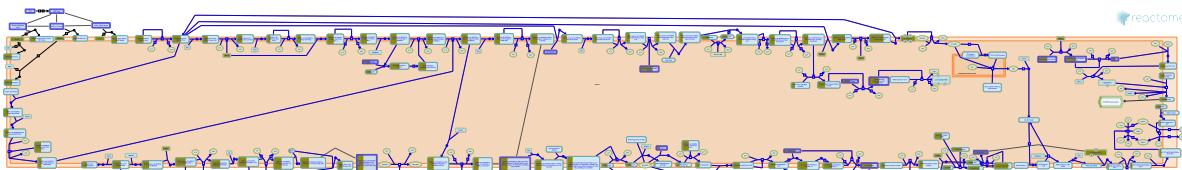
Edit history

Date	Action	Author
2011-03-15	Created	Orlic-Milacic M
2011-11-04	Authored	Orlic-Milacic M
2011-11-07	Edited	Matthews L, D'Eustachio P
2011-11-11	Reviewed	Xu W, Neckers LM
2018-12-05	Modified	Croft D

Entities found in this pathway (19)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31749	AKT2	P31751	AKT3	Q9Y243
EGFR	P00533	ERBB2	P04626	ERBB3	P21860-1
ERBB4	Q15303-1, Q15303-2, Q15303-3	GAB1	Q13480	GRB2	P62993-1
KRAS	P01111, P01116	PIK3CA	P42336	PLCG1	P19174
PRKACA	P17252	PRKCA	P17252	PRKCD	Q05655
RHOA	P61586	SHC1	P29353, P29353-1, P29353-2	SOS1	Q07889
SRC	P12931				

11. VEGFA-VEGFR2 Pathway (R-HSA-4420097)



Cellular compartments: plasma membrane.

Angiogenesis is the formation of new blood vessels from preexisting vasculature. One of the most important proangiogenic factors is vascular endothelial growth factor (VEGF). VEGF exerts its biologic effect through interaction with transmembrane tyrosine kinase receptors VEGFR, selectively expressed on vascular endothelial cells. VEGFA signaling through VEGFR2 is the major pathway that activates angiogenesis by inducing the proliferation, survival, sprouting and migration of endothelial cells (ECs), and also by increasing endothelial permeability (Lohela et al. 2009, Shibuya & Claesson-Welsh 2006, Claesson-Welsh & Welsh, 2013). The critical role of VEGFR2 in vascular development is highlighted by the fact that VEGFR2^{-/-} mice die at E8.5-9.5 due to defective development of blood islands, endothelial cells and haematopoietic cells (Shalaby et al. 1995).

References

- Olsson AK, Dimberg A, Kreuger J & Claesson-Welsh L (2006). VEGF receptor signalling - in control of vascular function. *Nat Rev Mol Cell Biol*, 7, 359-71. [🔗](#)
- Cross MJ, Dixelius J, Matsumoto T & Claesson-Welsh L (2003). VEGF-receptor signal transduction. *Trends Biochem Sci*, 28, 488-94. [🔗](#)
- Lohela M, Bry M, Tammela T & Alitalo K (2009). VEGFs and receptors involved in angiogenesis versus lymphangiogenesis. *Curr. Opin. Cell Biol.*, 21, 154-65. [🔗](#)
- Otruck ZK, Makarem JA & Shamseddine AI (2007). Vascular endothelial growth factor family of ligands and receptors: review. *Blood Cells Mol. Dis.*, 38, 258-68. [🔗](#)

Edit history

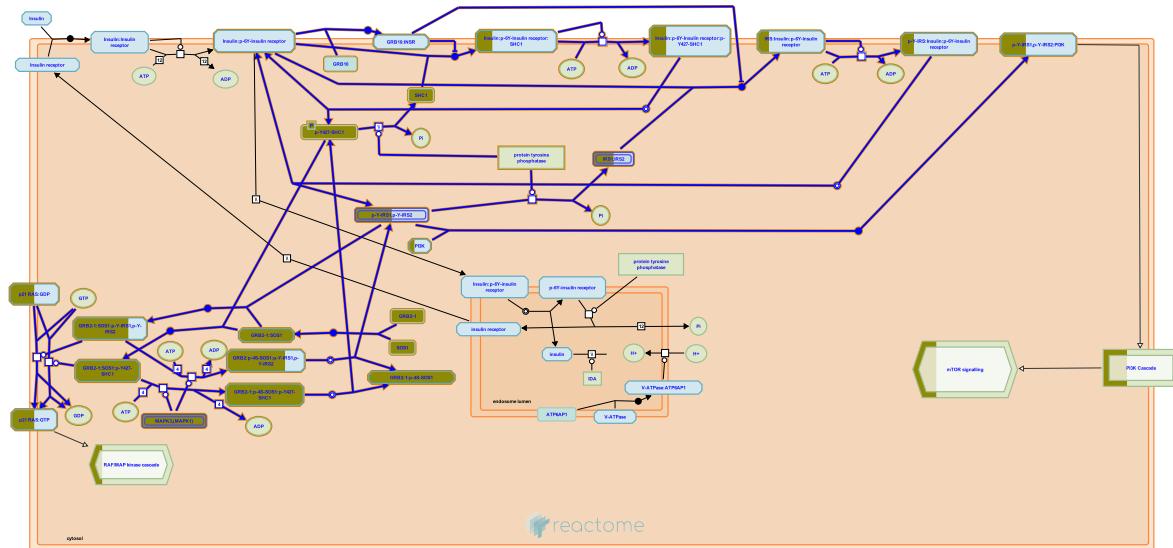
Date	Action	Author
2013-08-30	Edited	Garapati P V
2013-08-30	Authored	Garapati P V
2013-08-30	Created	Garapati P V
2014-05-12	Reviewed	Welsh M, Berger P, Ballmer-Hofer K
2018-11-29	Modified	Weiser D

Entities found in this pathway (24)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31749, P31751, Q9Y243	AKT2	P31751	AKT3	Q9Y243
CDC42	P60953	CTNNB1	P35222	KDR	P35968
KRAS	P01111, P01116	MAPK14	Q16539	MAPKAPK2	P49137
MLST8	Q9BVC4	MTOR	P42345	PAK1	O75914, Q13153
PDPK1	O15530	PIK3CA	P42336	PLCG1	P19174
PRKACA	P17252, P17612, P22612	PRKCA	P17252	PRKCD	Q05655

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
RAC1	P63000	RHOA	P61586	RICTOR	Q6R327
ROCK1	Q13464	SRC	P12931-1	VAV1	P15498

12. Insulin receptor signalling cascade (R-HSA-74751)



Cellular compartments: cytosol.

Autophosphorylation of the insulin receptor triggers a series of signalling events, mediated by SHC or IRS, and resulting in activation of the Ras/RAF and MAP kinase cascades. A second effect of the autophosphorylation of the insulin receptor is its internalisation into an endosome, which down-regulates its signalling activity.

References

Bevan P (2001). Insulin signalling. J Cell Sci, 114, 1429-30. [🔗](#)

Shepherd PR, Withers DJ & Siddle K (1998). Phosphoinositide 3-kinase: the key switch mechanism in insulin signalling. Biochem J, 333, 471-90. [🔗](#)

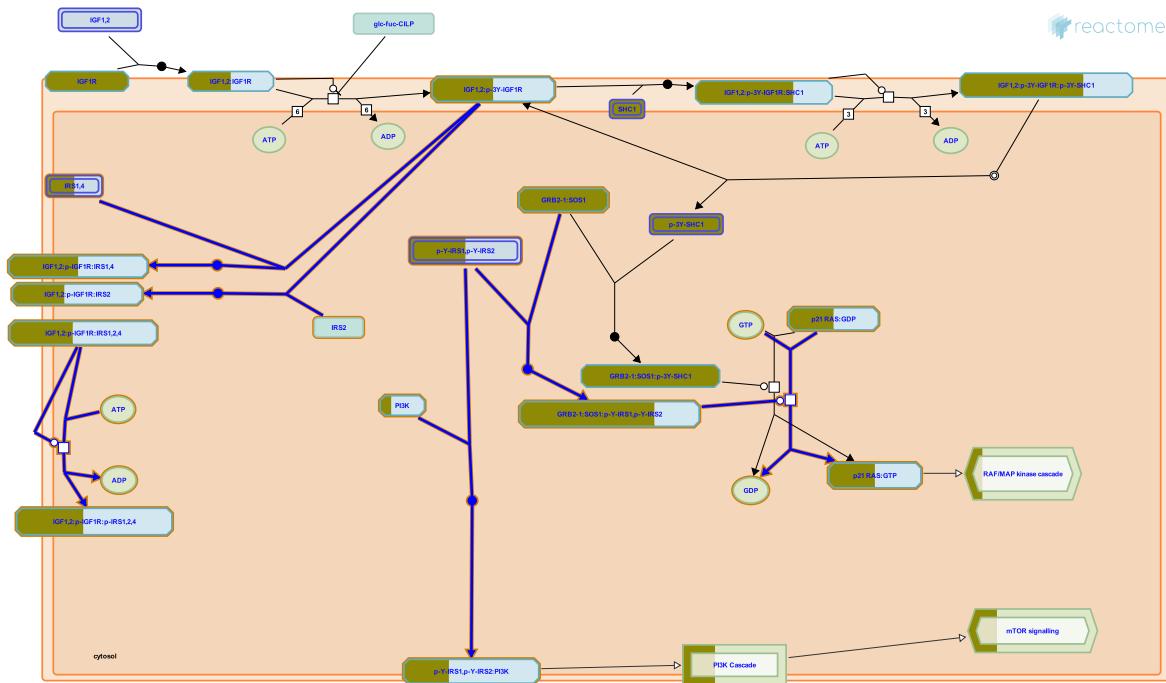
Edit history

Date	Action	Author
2003-07-31	Authored	Bevan AP
2003-07-31	Created	Bevan AP
2018-12-05	Modified	Croft D

Entities found in this pathway (19)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31751	AKT2	P31751	FGFR1	P11362-1, P11362-19
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5	FGFR3	P22607-1, P22607-2	FGFR4	P22455
FLT3	P36888	GAB1	Q13480	GAB2	Q9UQC2
GRB2	P62993-1	IRS1	P35568	KRAS	P01111, P01116
MAPK1	P28482	MAPK3	P27361	PDPK1	O15530
PIK3CA	P42336	PTPN11	Q06124	SHC1	P29353
SOS1	Q07889				

13. IRS-related events triggered by IGF1R (R-HSA-2428928)



Cellular compartments: cytosol, plasma membrane.

The phosphorylated type 1 insulin-like growth factor receptor phosphorylates IRS1, IRS2, IRS4 and possibly other IRS/DOK family members (reviewed in Pavelic et al. 2007, Chitnis et al. 2008, Maki et al. 2010, Parrella et al. 2010, Siddle et al. 2012). The phosphorylated IRS proteins serve as scaffolds that bind the effector molecules PI3K and GRB2:SOS. PI3K then activates PKB (AKT) signaling while GRB2:SOS activates RAS-RAF-MAPK signaling.

References

- Pavelic J, Matijevi T & Knezevi J (2007). Biological & physiological aspects of action of insulin-like growth factor peptide family. Indian J. Med. Res., 125, 511-22. [🔗](#)
- Parrella E & Longo VD (2010). Insulin/IGF-I and related signaling pathways regulate aging in nondividing cells: from yeast to the mammalian brain. ScientificWorldJournal, 10, 161-77. [🔗](#)
- Siddle K (2012). Molecular basis of signaling specificity of insulin and IGF receptors: neglected corners and recent advances. Front Endocrinol (Lausanne), 3, 34. [🔗](#)
- Maki RG (2010). Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer. J. Clin. Oncol., 28, 4985-95. [🔗](#)
- Annunziata M, Granata R & Ghigo E (2011). The IGF system. Acta Diabetol, 48, 1-9. [🔗](#)

Edit history

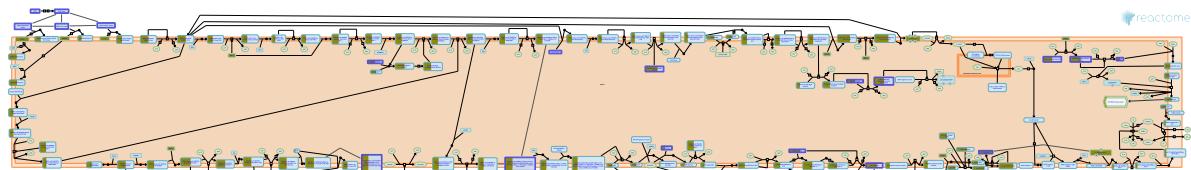
Date	Action	Author
2012-08-07	Edited	May B
2012-08-07	Authored	May B
2012-08-09	Created	May B
2012-11-10	Reviewed	Holzenberger M

Date	Action	Author
2018-12-05	Modified	Croft D

Entities found in this pathway (17)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31751	AKT2	P31751	FGFR1	P11362-1, P11362-19
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5	FGFR3	P22607-1, P22607-2	FGFR4	P22455
FLT3	P36888	GAB1	Q13480	GAB2	Q9UQC2
GRB2	P62993-1	IGF1R	P08069	IRS1	P35568
KRAS	P01111, P01116	PDPK1	O15530	PIK3CA	P42336
PTPN11	Q06124	SOS1	Q07889		

14. Signaling by VEGF (R-HSA-194138)



In normal development vascular endothelial growth factors (VEGFs) are crucial regulators of vascular development during embryogenesis (vasculogenesis) and blood-vessel formation in the adult (angiogenesis). In tumor progression, activation of VEGF pathways promotes tumor vascularization, facilitating tumor growth and metastasis. Abnormal VEGF function is also associated with inflammatory diseases including atherosclerosis, and hyperthyroidism. The members of the VEGF and VEGF-receptor protein families have distinct but overlapping ligand-receptor specificities, cell-type expression, and function. VEGF-receptor activation in turn regulates a network of signaling processes in the body that promote endothelial cell growth, migration and survival (Hicklin and Ellis, 2005; Shibuya and Claesson-Welsh, 2006).

Molecular features of the VGF signaling cascades are outlined in the figure below (from Olsson et al. 2006; Nature Publishing Group). Tyrosine residues in the intracellular domains of VEGF receptors 1, 2, and 3 are indicated by dark blue boxes; residues susceptible to phosphorylation are numbered. A circled R indicates that phosphorylation is regulated by cell state (VEGFR2), by ligand binding (VEGFR1), or by heterodimerization (VEGFR3). Specific phosphorylation sites (boxed numbers) bind signaling molecules (dark blue ovals), whose interaction with other cytosolic signaling molecules (light blue ovals) leads to specific cellular (pale blue boxes) and tissue-level (pink boxes) responses *in vivo*. Signaling cascades whose molecular details are unclear are indicated by dashed arrows. DAG, diacylglycerol; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; FAK, focal adhesion kinase; HPC, hematopoietic progenitor cell; HSP27, heat-shock protein-27; MAPK, mitogen-activated protein kinase; MEK, MAPK and ERK kinase; PI3K, phosphatidylinositol 3' kinase; PKC, protein kinase C; PLC γ , phospholipase C-gamma; Shb, SH2 and beta-cells; TSAd, T-cell-specific adaptor.

In the current release, the first events in these cascades - the interactions between VEGF proteins and their receptors - are annotated.

References

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

Hicklin DJ & Ellis LM (2005). Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*, 23, 1011-27. 

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

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. 

Edit history

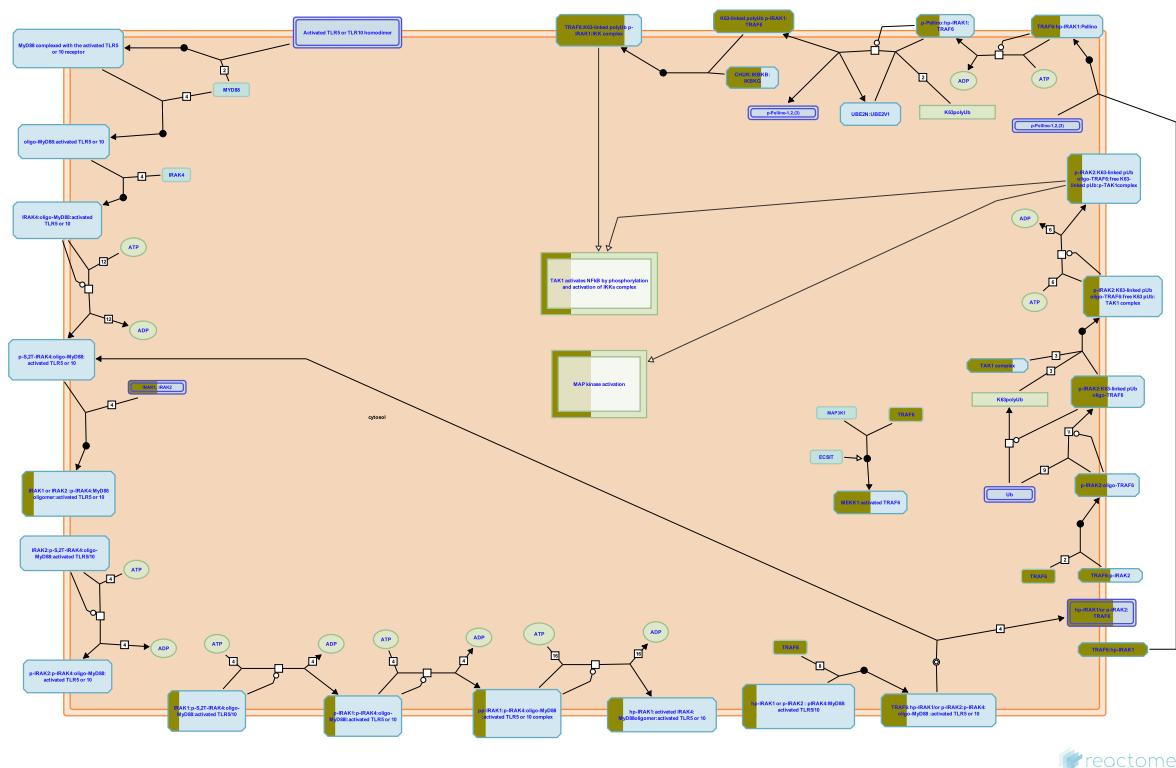
Date	Action	Author
2007-03-08	Created	Gopinathrao G

Date	Action	Author
2008-02-28	Reviewed	Claesson-Welsh L
2013-08-30	Edited	Garapati P V
2013-08-30	Authored	Garapati P V
2018-11-29	Modified	Weiser D

Entities found in this pathway (26)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31749, P31751, Q9Y243	AKT2	P31751	AKT3	Q9Y243
CDC42	P60953	CTNNB1	P35222	FLT1	P17948
FLT4	P35916	KDR	P35968	KRAS	P01111, P01116
MAPK14	Q16539	MAPKAPK2	P49137	MLST8	Q9BVC4
MTOR	P42345	PAK1	O75914, Q13153	PDPK1	O15530
PIK3CA	P42336	PLCG1	P19174	PRKACA	P17252, P17612, P22612
PRKCA	P17252	PRKCD	Q05655	RAC1	P63000
RHOA	P61586	RICTOR	Q6R327	ROCK1	Q13464
SRC	P12931-1	VAV1	P15498		

15. MyD88 cascade initiated on plasma membrane ([R-HSA-975871](#))



Mammalian myeloid differentiation factor 88 (MyD88) is Toll/interleukin (IL)-1 (TIR)-domain containing adapter protein which plays crucial role in TLR signaling. All TLRs, with only one exception of TLR3, can initiate downstream signaling through MyD88. In the MyD88 - dependent pathway, once the adaptor is bound to TLR it leads to recruitment of IL1 receptor associated kinase family IRAK which is followed by activation of tumour necrosis factor receptor-associated factor 6 (TRAF6) . TRAF6 is an ubiquitin E3 ligase which in turn induces TGF-beta activating kinase 1 (TAK1) auto phosphorylation. Once activated TAK1 can ultimately mediate the induction of the transcription factor NF- κ B or the mitogen-activated protein kinases (MAPK), such as JNK, p38 and ERK. This results in the translocation of the activated NF- κ B and MAPKs to the nucleus and the initiation of appropriate gene transcription leading to the production of many proinflammatory cytokines and antimicrobial peptides.

References

- Hasan U, Chaffois C, Gaillard C, Saulnier V, Merck E, Tancredi S, ... Bates EE (2005). Human TLR10 is a functional receptor, expressed by B cells and plasmacytoid dendritic cells, which activates gene transcription through MyD88. *J Immunol*, 174, 2942-50. 

Zhang Z, Louboutin JP, Weiner DJ, Goldberg JB & Wilson JM (2005). Human airway epithelial cells sense *Pseudomonas aeruginosa* infection via recognition of flagellin by Toll-like receptor 5. *Infect Immun*, 73, 7151-60. 

Edit history

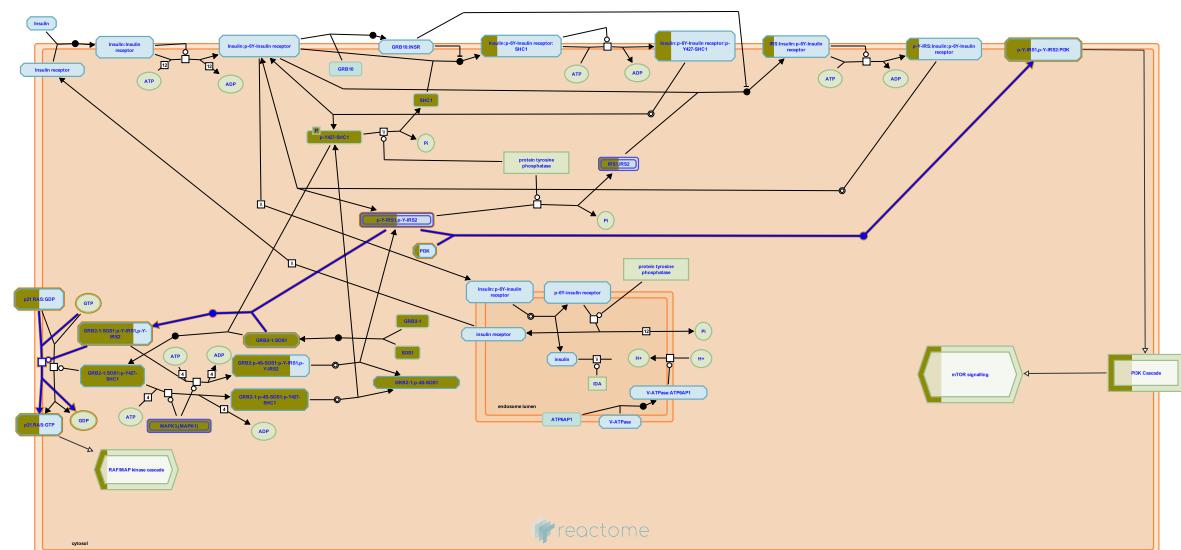
Date	Action	Author
2010-10-06	Authored	Shamovsky V
2010-10-06	Created	Shamovsky V

Date	Action	Author
2011-02-10	Reviewed	Gillespie ME
2011-08-04	Reviewed	Li L
2011-08-12	Edited	Shamovsky V
2018-12-05	Modified	Croft D

Entities found in this pathway (31)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATF2	P15336	BTRC	Q9Y297	CHUK	O15111
DUSP6	Q16828	FOS	P01100	IKBKB	O14920
IRAK1	P51617	JUN	P05412	MAP2K1	Q02750
MAP2K3	P46734	MAP2K4	P45985	MAP2K7	O14733
MAP3K7	O43318	MAP3K8	P41279	MAPK1	P28482
MAPK14	Q16539	MAPK3	P27361	MAPK8	P45983
MAPK9	P45984	MAPKAPK2	P49137	NFKB1	P19838
NFKB2	Q00653	REL	Q00653	RELA	Q04206
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA5	O75582	TAB1	Q15750	TAB2	Q9NYJ8
TRAF6	Q9Y4K3				

16. IRS-mediated signalling (R-HSA-112399)



Cellular compartments: plasma membrane, cytosol.

Release of phospho-IRS from the insulin receptor triggers a cascade of signalling events via PI3K, SOS, RAF and the MAP kinases.

References

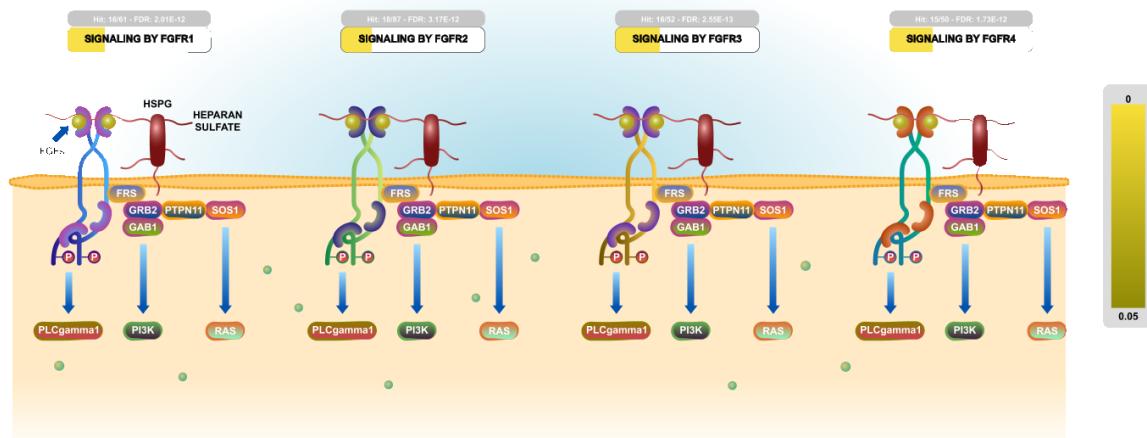
Edit history

Date	Action	Author
2004-04-29	Authored	Charalambous M
2004-04-29	Created	Charalambous M
2018-12-05	Modified	Croft D

Entities found in this pathway (16)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31751	AKT2	P31751	FGFR1	P11362-1, P11362-19
FGFR2	P21802-1, P21802-18, P21802-3, P21802-5	FGFR3	P22607-1, P22607-2	FGFR4	P22455
FLT3	P36888	GAB1	Q13480	GAB2	Q9UQC2
GRB2	P62993-1	IRS1	P35568	KRAS	P01111, P01116
PDPK1	O15530	PIK3CA	P42336	PTPN11	Q06124
SOS1	Q07889				

17. Signaling by FGFR (R-HSA-190236)



The 22 members of the fibroblast growth factor (FGF) family of growth factors mediate their cellular responses by binding to and activating the different isoforms encoded by the four receptor tyrosine kinases (RTKs) designated FGFR1, FGFR2, FGFR3 and FGFR4. These receptors are key regulators of several developmental processes in which cell fate and differentiation to various tissue lineages are determined. Unlike other growth factors, FGFs act in concert with heparin or heparan sulfate proteoglycan (HSPG) to activate FGFRs and to induce the pleiotropic responses that lead to the variety of cellular responses induced by this large family of growth factors. An alternative, FGF-independent, source of FGFR activation originates from the interaction with cell adhesion molecules, typically in the context of interactions on neural cell membranes and is crucial for neuronal survival and development.

Upon ligand binding, receptor dimers are formed and their intrinsic tyrosine kinase is activated causing phosphorylation of multiple tyrosine residues on the receptors. These then serve as docking sites for the recruitment of SH2 (src homology-2) or PTB (phosphotyrosine binding) domains of adaptors, docking proteins or signaling enzymes. Signaling complexes are assembled and recruited to the active receptors resulting in a cascade of phosphorylation events.

This leads to stimulation of intracellular signaling pathways that control cell proliferation, cell differentiation, cell migration, cell survival and cell shape, depending on the cell type or stage of maturation.

References

- Eswarakumar VP, Lax I & Schlessinger J (2005). Cellular signaling by fibroblast growth factor receptors. *Cytokine Growth Factor Rev*, 16, 139-49. [🔗](#)
- Schlessinger J (2004). Common and distinct elements in cellular signaling via EGF and FGF receptors. *Science*, 306, 1506-7. [🔗](#)
- Ornitz DM & Marie PJ (2002). FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. *Genes Dev*, 16, 1446-65. [🔗](#)
- Dailey L, Ambrosetti D, Mansukhani A & Basilico C (2005). Mechanisms underlying differential responses to FGF signaling. *Cytokine Growth Factor Rev*, 16, 233-47. [🔗](#)

Zhang X, Ibrahimi OA, Olsen SK, Umemori H, Mohammadi M & Ornitz DM (2006). Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. *J Biol Chem*, 281, 15694-700. [View](#)

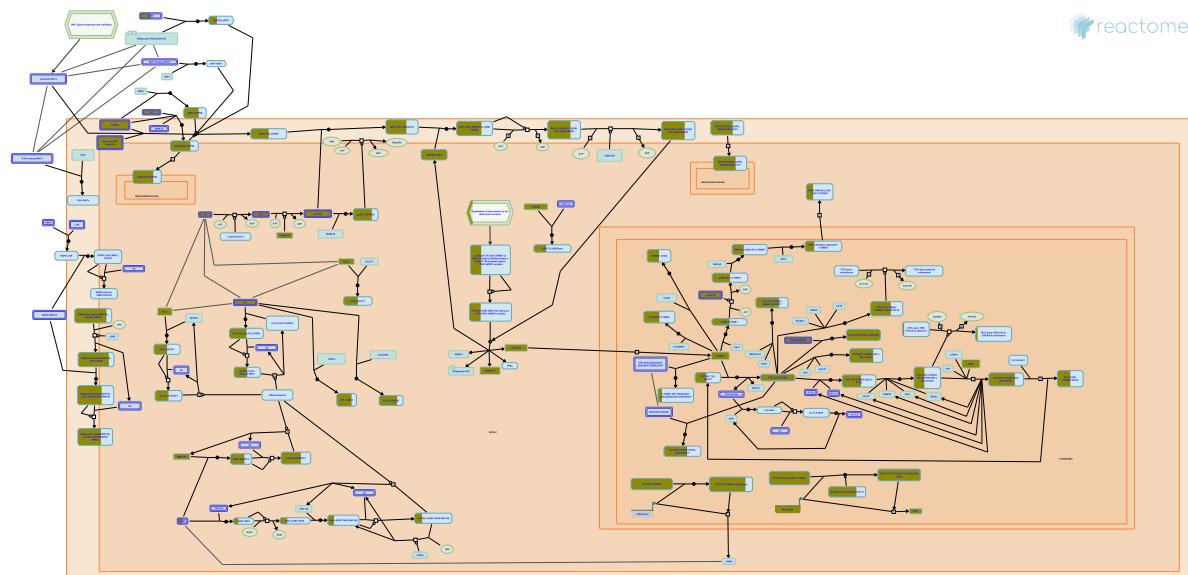
Edit history

Date	Action	Author
2006-12-18	Created	de Bono B
2007-01-10	Authored	de Bono B
2007-02-07	Reviewed	Mohammadi M
2007-02-11	Edited	D'Eustachio P, de Bono B
2011-08-26	Reviewed	Gotoh N
2018-11-29	Modified	Weiser D

Entities found in this pathway (16)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BRAF	P15056	FGFR1	P11362-1, P11362-19	FGFR2	P21802-1, P21802-18, P21802-3, P21802-5
FGFR3	P22607-1, P22607-2	FGFR4	P22455	GAB1	Q13480
GRB2	P62993-1	KRAS	P01111, P01116	MAPK1	P28482
MAPK3	P27361	PIK3CA	P42336	PLCG1	P19174
PTPN11	Q06124	SHC1	P29353-2, P29353-3	SOS1	Q07889
SRC	P12931-1				

18. TCF dependent signaling in response to WNT (R-HSA-201681)



Cellular compartments: cytosol, extracellular region, nucleoplasm.

19 WNT ligands and 10 FZD receptors have been identified in human cells; interactions amongst these ligands and receptors vary in a developmental and tissue-specific manner and lead to activation of so-called 'canonical' and 'non-canonical' WNT signaling. In the canonical WNT signaling pathway, binding of a WNT ligand to the Frizzled (FZD) and lipoprotein receptor-related protein (LRP) receptors results in the inactivation of the destruction complex, the stabilization and nuclear translocation of beta-catenin and subsequent activation of T-cell factor/lymphoid enhancing factor (TCF/LEF)-dependent transcription. Transcriptional activation in response to canonical WNT signaling controls processes such as cell fate, proliferation and self renewal of stem cells, as well as contributing to oncogenesis (reviewed in MacDonald et al, 2009; Saito-Diaz et al, 2013; Kim et al, 2013).

References

- MacDonald BT, Tamai K & He X (2009). Wnt/beta-catenin signaling: components, mechanisms, and diseases. *Dev Cell*, 17, 9-26. [🔗](#)
- Saito-Diaz K, Chen TW, Wang X, Thorne CA, Wallace HA, Page-McCaw A & Lee E (2013). The way Wnt works: Components and mechanism. *Growth Factors*, 31, 1-31. [🔗](#)
- Kim W, Kim M & Jho EH (2013). Wnt/?-catenin signalling: from plasma membrane to nucleus. *Biochem. J.*, 450, 9-21. [🔗](#)

Edit history

Date	Action	Author
2007-09-04	Edited	Matthews L
2007-09-11	Created	Matthews L
2013-08-24	Authored	Rothfels K
2013-10-03	Edited	Gillespie ME
2014-01-22	Reviewed	Rajakulendran N

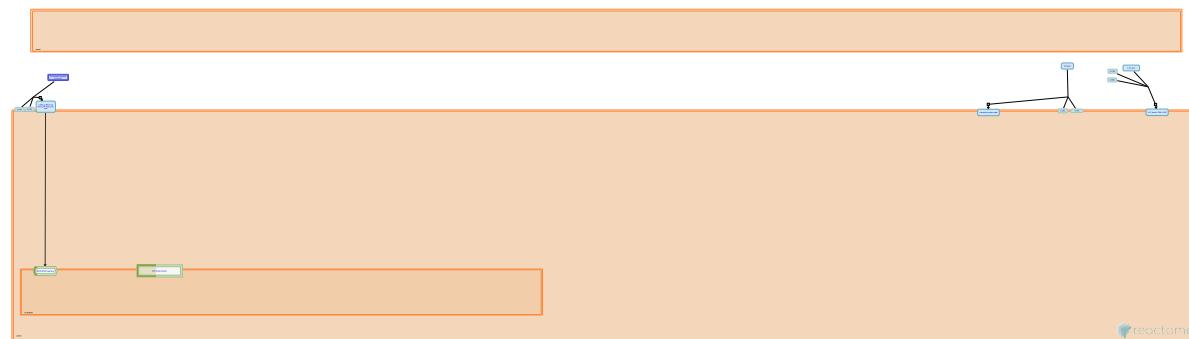
Date	Action	Author
2014-02-15	Reviewed	van Amerongen R
2014-04-22	Reviewed	Kikuchi A
2018-12-05	Modified	Croft D

Entities found in this pathway (32)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31749	AKT2	P31751	AXIN1	O15169
BTRC	Q9Y297	CREBBP	Q92793	CSNK1A1	P48729
CSNK1E	P49674	CTNNB1	P35222	DKK1	O94907
DKK2	Q9UBU2	DKK4	Q9UBT3	DVL1	O14640
DVL2	O14641, Q92997	DVL3	Q92997	EP300	Q09472
FZD1	Q9UP38	FZD2	Q14332	FZD4	Q9ULV1
FZD5	Q13467	FZD6	O60353	FZD8	Q9H461
GSK3A	P49841	GSK3B	P49841	LEF1	Q9UJU2
LRP5	O75197	LRP6	O75581	MYC	P01106
SFRP1	Q8N474	SMURF2	Q9HAU4	TCF7	P36402
TCF7L1	Q9HCS4	TCF7L2	Q9NQB0		

Input	Ensembl Id
MYC	ENSG00000136997

19. Interleukin-17 signaling (R-HSA-448424)



Interleukin-17 (IL17) is a family of cytokines (Kawaguchi et al. 2004, Gu et al. 2013). IL17A, the founding member of the family is able to induce the production of other cytokines and chemokines, such as IL6, IL8, and granulocyte colony-stimulating factor (G-CSF) in a variety of cell types, including activated T-cells. It plays a pivotal role in host defenses in response to microbial infection and is involved in the pathogenesis of autoimmune diseases and allergic syndromes. IL17 activates several downstream signaling pathways including NFkB, MAPKs and C/EBPs, inducing the expression of antibacterial peptides, proinflammatory chemokines and cytokines and matrix metalloproteases (MMPs). IL17 can stabilize the mRNA of genes induced by TNF-alpha. IL17 signal transduction is mediated by the cytosolic adaptor molecule ACT1 (also known as CIKS).

The receptor for IL17D is unknown (Gu et al. 2013).

References

Gu C, Wu L & Li X (2013). IL-17 family: cytokines, receptors and signaling. *Cytokine*, 64, 477-85. [🔗](#)

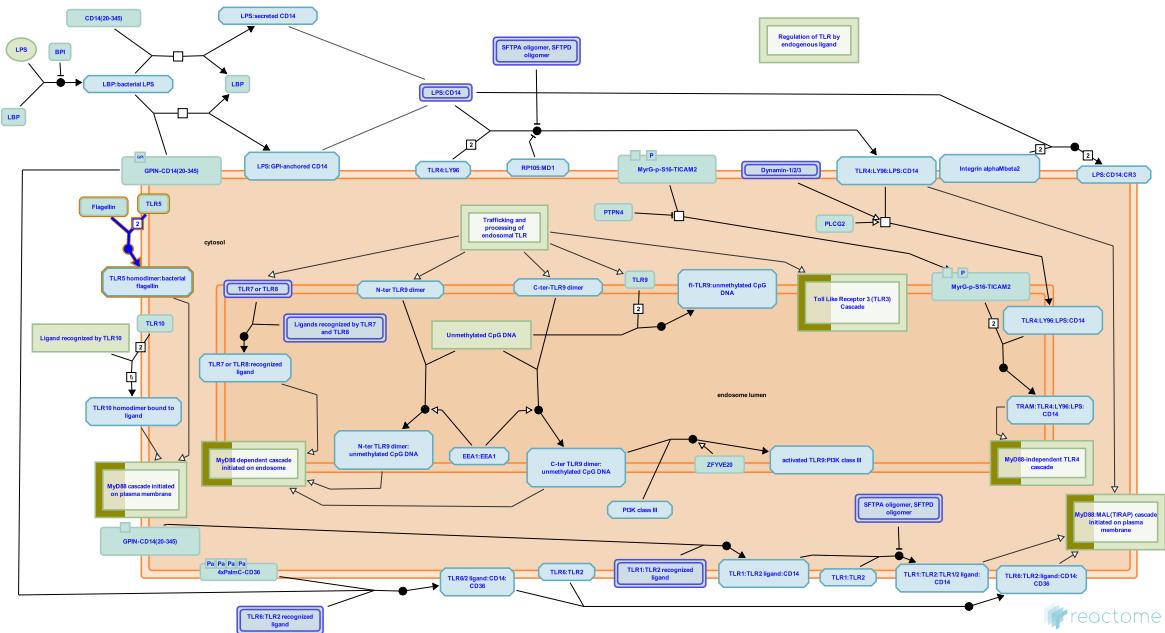
Edit history

Date	Action	Author
2009-11-24	Created	Jupe S
2014-06-04	Authored	Jupe S
2016-01-28	Edited	Jupe S
2016-01-28	Reviewed	Meldal BH
2018-12-05	Modified	Croft D

Entities found in this pathway (28)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATF2	P15336	BTRC	Q9Y297	CHUK	O15111
DUSP6	Q16828	FOS	P01100	IKBKB	O14920
IRAK1	P51617	JUN	P05412	MAP2K1	Q02750
MAP2K3	P46734	MAP2K4	P45985	MAP2K7	O14733
MAP3K7	O43318	MAP3K8	P41279	MAPK1	P28482
MAPK14	Q16539	MAPK3	P27361	MAPK8	P45983
MAPK9	P45984	MAPKAPK2	P49137	NFKB1	P19838
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA5	O75582	TAB1	Q15750	TAB2	Q9NYJ8
TRAF6	Q9Y4K3				

20. Toll Like Receptor 5 (TLR5) Cascade (R-HSA-168176)



TLR5 is the receptor for flagellin, the protein that forms bacterial flagella. Unlike most other Pathogen-Associated Molecular Patterns (PAMPs), flagellin does not undergo any posttranslational modifications that would distinguish it from cellular proteins. However, flagellin is extremely conserved at its amino- and carboxyl-termini, which presumably explains why it was selected as a ligand for innate immune recognition. TLR5 is expressed on epithelial cells as well as on macrophages and dendritic cells. Expression of TLR5 on intestinal epithelium is polarized such that TLR5 is expressed only on the basolateral side of the cell, as pathogenic but not commensal microbes cross the epithelial barrier. This ensures that innate immune responses are confined to pathogenic but not commensal microbes (Paul 2004; Hayashi et al. 2001; Gewirtz et al. 2001).

References

- Hayashi F, Smith KD, Ozinsky A, Hawn TR, Yi EC, Goodlett DR, ... Aderem A (2001). The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. *Nature*, 410, 1099-103. [🔗](#)
- Gewirtz AT, Navas TA, Lyons S, Godowski PJ & Madara JL (2001). Cutting edge: bacterial flagellin activates basolaterally expressed TLR5 to induce epithelial proinflammatory gene expression. *J Immunol*, 167, 1882-5. [🔗](#)
- Paul W (2003). *Innate Immune System, Fundamental Immunology*, 497-518.

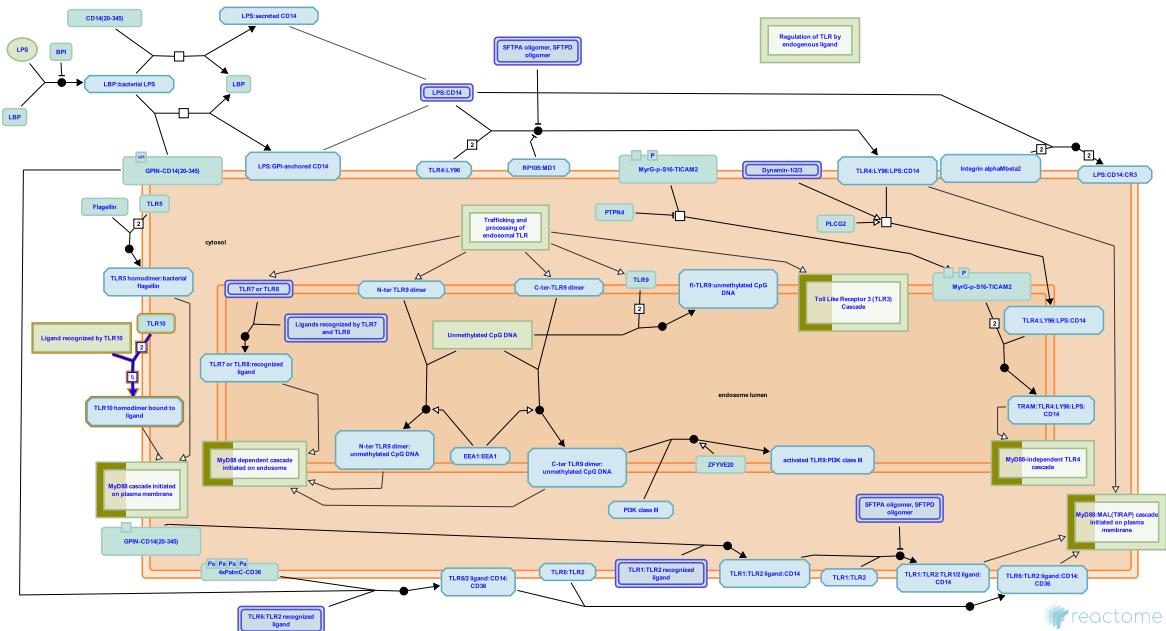
Edit history

Date	Action	Author
2005-11-10	Authored	Luo F
2005-11-10	Created	Gillespie ME
2006-10-31	Reviewed	Gale M Jr
2011-02-10	Reviewed	Gillespie ME
2011-08-12	Edited	Shamovsky V
2018-12-05	Modified	Croft D

Entities found in this pathway (31)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATF2	P15336	BTRC	Q9Y297	CHUK	O15111
DUSP6	Q16828	FOS	P01100	IKBKB	O14920
IRAK1	P51617	JUN	P05412	MAP2K1	Q02750
MAP2K3	P46734	MAP2K4	P45985	MAP2K7	O14733
MAP3K7	O43318	MAP3K8	P41279	MAPK1	P28482
MAPK14	Q16539	MAPK3	P27361	MAPK8	P45983
MAPK9	P45984	MAPKAPK2	P49137	NFKB1	P19838
NFKB2	Q00653	REL	Q00653	RELA	Q04206
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA5	O75582	TAB1	Q15750	TAB2	Q9NYJ8
TRAF6	Q9Y4K3				

21. Toll Like Receptor 10 (TLR10) Cascade (R-HSA-168142)



Little is known about TLR10 ligands. It has been established that the receptor homodimerizes upon binding and signals in an MyD88-dependent manner (Hasan U et al 2005; Nyman T et al 2008). It may also heterodimerize with TLRs 1 and 2. It is expressed in a restricted fashion as a highly N-glycosylated protein detectable in B cells and dendritic cells.

References

Hasan U, Chaffois C, Gaillard C, Saulnier V, Merck E, Tancredi S, ... Bates EE (2005). Human TLR10 is a functional receptor, expressed by B cells and plasmacytoid dendritic cells, which activates gene transcription through MyD88. *J Immunol*, 174, 2942-50. 

Nyman T, Stenmark P, Flodin S, Johansson I, Hammarström M & Nordlund P (2008). The crystal structure of the human toll-like receptor 10 cytoplasmic domain reveals a putative signaling dimer. *J Biol Chem*, 283, 11861-5. 

Edit history

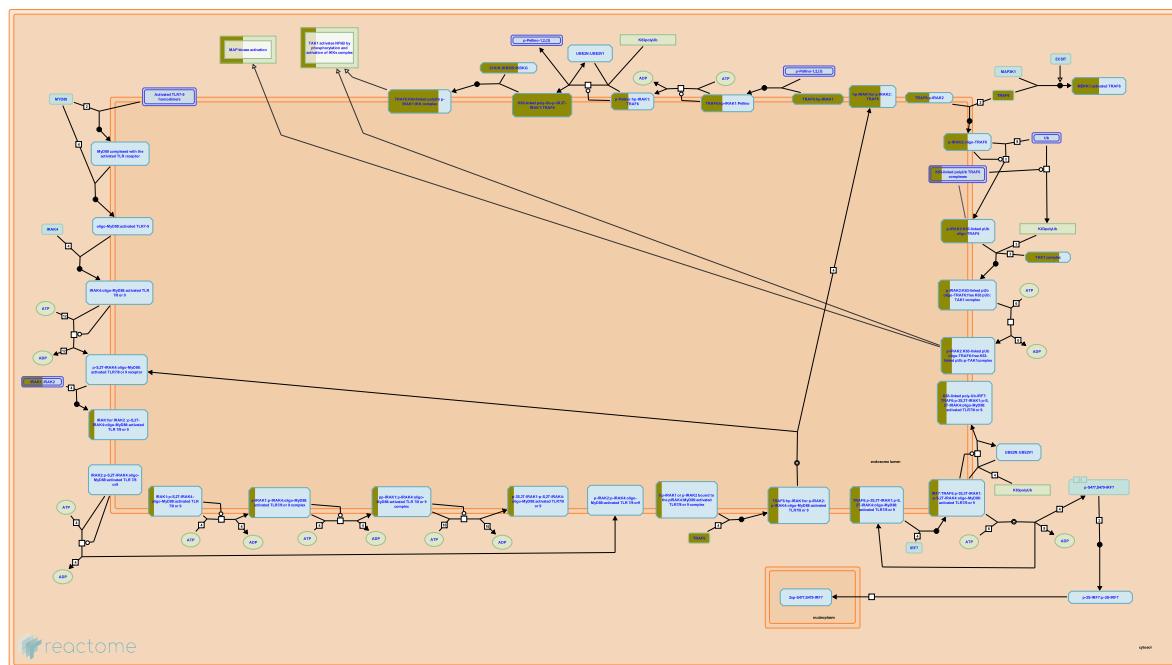
Date	Action	Author
2005-11-10	Authored	Luo F
2005-11-10	Created	Gillespie ME
2006-10-31	Reviewed	Gale M Jr
2011-02-10	Reviewed	Gillespie ME
2011-08-12	Edited	Shamovsky V
2018-12-05	Modified	Croft D

Entities found in this pathway (31)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATF2	P15336	BTRC	Q9Y297	CHUK	O15111
DUSP6	Q16828	FOS	P01100	IKBKB	O14920

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IRAK1	P51617	JUN	P05412	MAP2K1	Q02750
MAP2K3	P46734	MAP2K4	P45985	MAP2K7	O14733
MAP3K7	O43318	MAP3K8	P41279	MAPK1	P28482
MAPK14	Q16539	MAPK3	P27361	MAPK8	P45983
MAPK9	P45984	MAPKAPK2	P49137	NFKB1	P19838
NFKB2	Q00653	REL	Q00653	RELA	Q04206
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA5	O75582	TAB1	Q15750	TAB2	Q9NYJ8
TRAF6	Q9Y4K3				

22. MyD88 dependent cascade initiated on endosome (R-HSA-975155)



Cellular compartments: cytosol, endosome membrane, nucleoplasm.

Upon binding of their ligands, TLR7/8 and TLR9 recruit a cytoplasmic adaptor MyD88 and IRAKs, downstream of which the signaling pathways are divided to induce either inflammatory cytokines or type I IFNs.

References

- Cherfils-Vicini J, Platonova S, Gillard M, Laurans L, Validire P, Caliandro R, ... Cremer I (2010). Triggering of TLR7 and TLR8 expressed by human lung cancer cells induces cell survival and chemoresistance. *J. Clin. Invest.*, 120, 1285-97. [🔗](#)
- Gangloff M & Gay NJ (2004). MD-2: the Toll 'gatekeeper' in endotoxin signalling. *Trends Biochem Sci*, 29, 294-300. [🔗](#)
- Hanten JA, Vasilakos JP, Riter CL, Neys L, Lipson KE, Alkan SS & Birmachu W (2008). Comparison of human B cell activation by TLR7 and TLR9 agonists. *BMC Immunol.*, 9, 39. [🔗](#)

Edit history

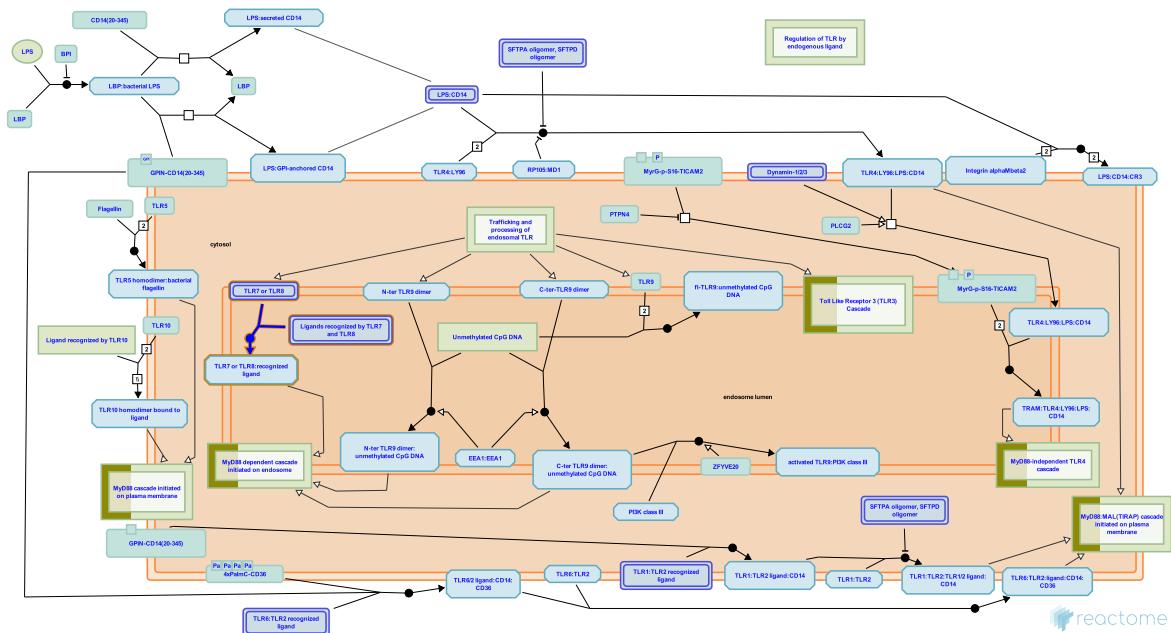
Date	Action	Author
2005-08-16	Authored	de Bono B
2010-09-22	Created	Shamovsky V
2010-10-29	Reviewed	Gillespie ME
2010-11-15	Edited	Shamovsky V
2018-12-05	Modified	Croft D

Entities found in this pathway (31)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATF2	P15336	BTRC	Q9Y297	CHUK	O15111

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
DUSP6	Q16828	FOS	P01100	IKBKB	O14920
IRAK1	P51617	JUN	P05412	MAP2K1	Q02750
MAP2K3	P46734	MAP2K4	P45985	MAP2K7	O14733
MAP3K7	O43318	MAP3K8	P41279	MAPK1	P28482
MAPK14	Q16539	MAPK3	P27361	MAPK8	P45983
MAPK9	P45984	MAPKAPK2	P49137	NFKB1	P19838
NFKB2	Q00653	REL	Q00653	RELA	Q04206
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA5	O75582	TAB1	Q15750	TAB2	Q9NYJ8
TRAF6	Q9Y4K3				

23. Toll Like Receptor 7/8 (TLR7/8) Cascade (R-HSA-168181)



Cellular compartments: cytosol, endosome membrane, nucleoplasm.

RNA can serve as a danger signal, both in its double-stranded form (that is associated with viral infection), as well as single-stranded RNA (ssRNA). Specifically, guanosine (G)- and uridine (U)-rich ssRNA oligonucleotides derived from human immunodeficiency virus-1 (HIV-1), for example, stimulate dendritic cells (DC) and macrophages to secrete interferon-alpha and proinflammatory, as well as regulatory, cytokines. This has been found to be mediated by TLR7, as well as TLR8. Separate studies showed that imidazoquinoline compounds (e.g. imiquimod and R-848, low-molecular-weight immune response modifiers that can induce the synthesis of interferon-alpha) also exert their effects in a MyD88-dependent fashion independently through TLR7 and 8 (Heil et al. 2004).

References

Heil F, Hemmi H, Hochrein H, Ampenberger F, Kirschning C, Akira S, ... Bauer S (2004). Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science*, 303, 1526-9. ↗

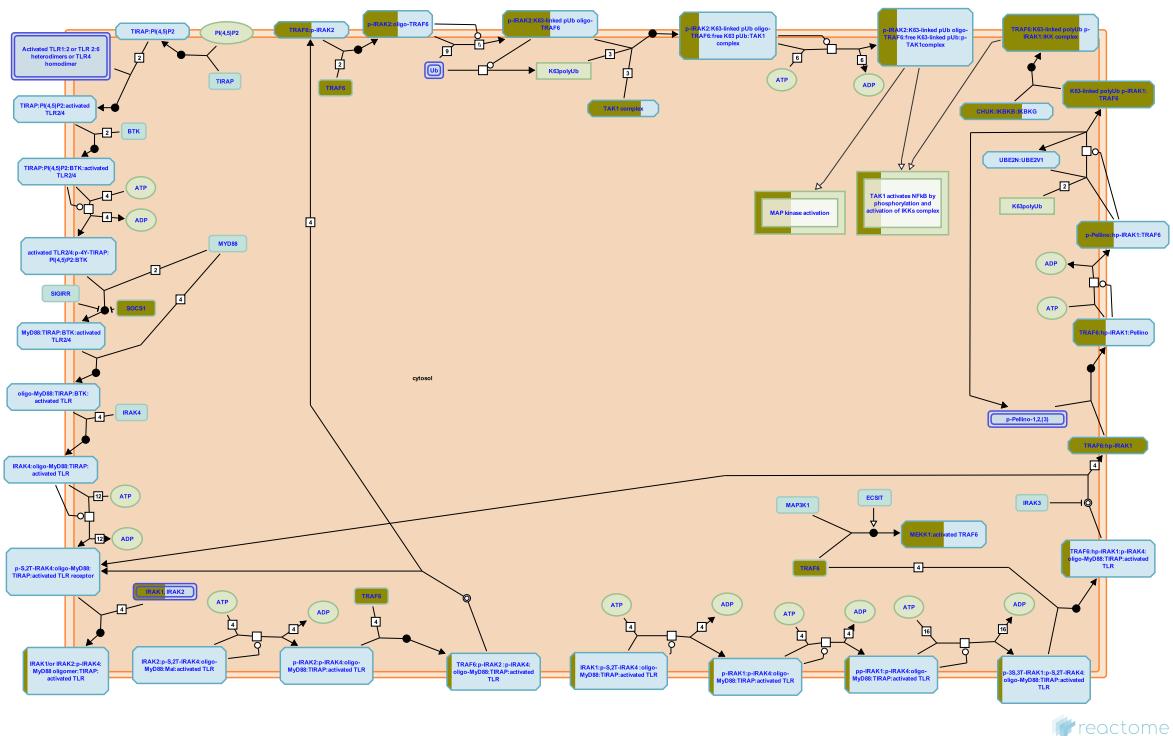
Edit history

Date	Action	Author
2005-11-10	Authored	Luo F
2005-11-10	Created	Gillespie ME
2006-10-31	Reviewed	Gale M Jr
2010-02-22	Revised	Shamovsky V
2010-10-29	Reviewed	Gillespie ME
2010-11-15	Edited	Shamovsky V
2018-12-05	Modified	Croft D

Entities found in this pathway (31)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATF2	P15336	BTRC	Q9Y297	CHUK	O15111
DUSP6	Q16828	FOS	P01100	IKBKB	O14920
IRAK1	P51617	JUN	P05412	MAP2K1	Q02750
MAP2K3	P46734	MAP2K4	P45985	MAP2K7	O14733
MAP3K7	O43318	MAP3K8	P41279	MAPK1	P28482
MAPK14	Q16539	MAPK3	P27361	MAPK8	P45983
MAPK9	P45984	MAPKAPK2	P49137	NFKB1	P19838
NFKB2	Q00653	REL	Q00653	RELA	Q04206
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA5	O75582	TAB1	Q15750	TAB2	Q9NYJ8
TRAF6	Q9Y4K3				

24. MyD88:Mal(TIRAP) cascade initiated on plasma membrane (R-HSA-166058)



The first known downstream component of TLR4 and TLR2 signaling is the adaptor MyD88. Another adaptor MyD88-adaptor-like (Mal; also known as TIR-domain-containing adaptor protein or TIRAP) has also been described for TLR4 and TLR2 signaling. MyD88 comprises an N-terminal Death Domain (DD) and a C-terminal TIR, whereas Mal lacks the DD. The TIR homotypic interactions bring adapters into contact with the activated TLRs, whereas the DD modules recruit serine-/threonine kinases such as interleukin-1-receptor-associated kinase (IRAK). Recruitment of these protein kinases is accompanied by phosphorylation, which in turn results in the interaction of IRAKs with TNF-receptor-associated factor 6 (TRAF6). The oligomerization of TRAF6 activates TAK1, a member of the MAP3-kinase family, and this leads to the activation of the I κ B kinases. These kinases, in turn, phosphorylate I κ B, leading to its proteolytic degradation and the translocation of NF- κ B to the nucleus. Concomitantly, members of the activator protein-1 (AP-1) transcription factor family, Jun and Fos, are activated, and both AP-1 transcription factors and NF- κ B are required for cytokine production, which in turn produces downstream inflammatory effects.

References

Gangloff M & Gay NJ (2004). MD-2: the Toll 'gatekeeper' in endotoxin signalling. Trends Biochem Sci, 29, 294-300. [View](#)

Edit history

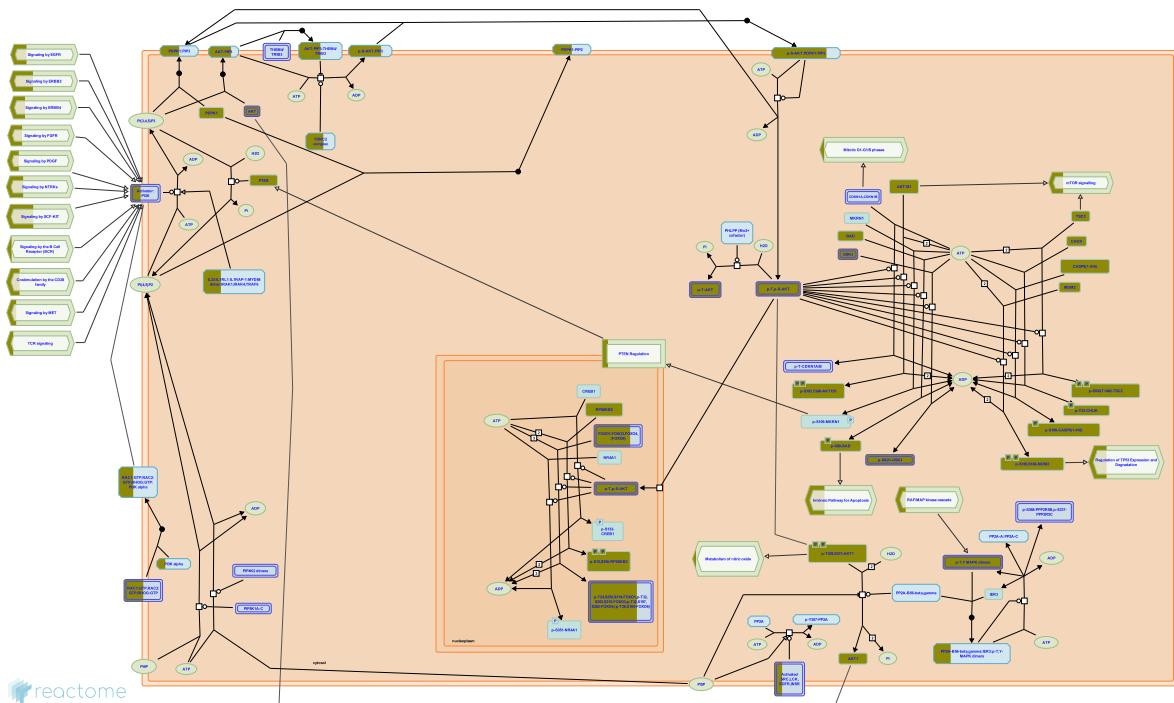
Date	Action	Author
2005-08-16	Authored	de Bono B
2005-08-16	Created	de Bono B
2006-04-24	Reviewed	Gay NJ
2010-11-30	Reviewed	Gillespie ME
2012-11-02	Revised	Shamovsky V

Date	Action	Author
2012-11-06	Edited	Shamovsky V
2012-11-16	Reviewed	Napetschnig J
2018-12-05	Modified	Croft D

Entities found in this pathway (32)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
ATF2	P15336	BTRC	Q9Y297	CHUK	O15111
DUSP6	Q16828	FOS	P01100	IKBKB	O14920
IRAK1	P51617	JUN	P05412	MAP2K1	Q02750
MAP2K3	P46734	MAP2K4	P45985	MAP2K7	O14733
MAP3K7	O43318	MAP3K8	P41279	MAPK1	P28482
MAPK14	Q16539	MAPK3	P27361	MAPK8	P45983
MAPK9	P45984	MAPKAPK2	P49137	NFKB1	P19838
NFKB2	Q00653	REL	Q00653	RELA	Q04206
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA5	O75582	SOCS1	O15524	TAB1	Q15750
TAB2	Q9NYJ8	TRAF6	Q9Y4K3		

25. PIP3 activates AKT signaling (R-HSA-1257604)



Signaling by AKT is one of the key outcomes of receptor tyrosine kinase (RTK) activation. AKT is activated by the cellular second messenger PIP3, a phospholipid that is generated by PI3K. In unstimulated cells, PI3K class IA enzymes reside in the cytosol as inactive heterodimers composed of p85 regulatory subunit and p110 catalytic subunit. In this complex, p85 stabilizes p110 while inhibiting its catalytic activity. Upon binding of extracellular ligands to RTKs, receptors dimerize and undergo autophosphorylation. The regulatory subunit of PI3K, p85, is recruited to phosphorylated cytosolic RTK domains either directly or indirectly, through adaptor proteins, leading to a conformational change in the PI3K IA heterodimer that relieves inhibition of the p110 catalytic subunit. Activated PI3K IA phosphorylates PIP2, converting it to PIP3; this reaction is negatively regulated by PTEN phosphatase. PIP3 recruits AKT to the plasma membrane, allowing TORC2 to phosphorylate a conserved serine residue of AKT. Phosphorylation of this serine induces a conformation change in AKT, exposing a conserved threonine residue that is then phosphorylated by PDK1 (PDK1). Phosphorylation of both the threonine and the serine residue is required to fully activate AKT. The active AKT then dissociates from PIP3 and phosphorylates a number of cytosolic and nuclear proteins that play important roles in cell survival and metabolism. For a recent review of AKT signaling, please refer to Manning and Cantley, 2007.

References

Edit history

Date	Action	Author
2007-11-08	Reviewed	Greene LA
2011-05-02	Created	Orlic-Milacic M
2012-06-21	Revised	Orlic-Milacic M
2012-08-13	Reviewed	Yuzugullu H, Thorpe L, Zhao JJ
2018-11-29	Modified	Weiser D

Entities found in this pathway (51)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31749, P31751, Q9Y243	AKT1S1	Q96B36	AKT2	P31751
AKT3	Q9Y243	ATF2	P15336	BAD	Q92934
CASP9	P55211	CHUK	O15111	EGFR	P00533
EGR1	P18146	ERBB2	P04626	ERBB3	P21860-1
ERBB4	Q15303-1, Q15303-2	FGFR1	P11362-1, P11362-19	FGFR2	P21802-1, P21802-18, P21802-3, P21802-5
FGFR3	P22607-1, P22607-2	FGFR4	P22455	FOXO1	Q12778
FOXO3	O43524	FOXO4	P98177	GAB1	Q13480
GRB2	P62993-1	GSK3A	P49840, P49841	GSK3B	P49841
IRAK1	P51617	IRS1	P35568	JUN	P05412
KIT	P10721	MAPK1	P28482	MAPK3	P27361
MDM2	Q00987	MET	P08581	MLST8	Q9BVC4
MTOR	P42345	PDGFRA	P16234	PDGFRB	P09619
PDPK1	O15530	PIK3CA	P42336	PTEN	P60484
PTPN11	Q06124	RAC1	P63000	RAC2	P15153
RHEB	Q15382	RICTOR	Q6R327	RPS6KB2	Q9UBS0
RPTOR	Q8N122	SRC	P12931, P12931-1	TP53	P04637
TRAF6	Q9Y4K3	TSC2	P49815	VAV1	P15498
Input	Ensembl Id				
PTEN	ENSG00000171862, ENST00000371953				

6. Identifiers found

Below is a list of the input identifiers that have been found or mapped to an equivalent element in Reactome, classified by resource.

Entities (190)

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
AKT1	P31749, P31751, Q9Y243	AKT1S1	Q96B36	AKT2	P31751
AKT3	Q9Y243	ARAF	P10398	ARHGAP24	Q8N264
ATF2	P15336	AXIN1	O15169	BAD	Q92934
BAX	Q07812	BCL2	P10415	BMPR2	Q13873
BRAF	P15056	BTRC	Q9Y297	CASP3	P42574
CASP8	Q14790	CASP9	P55211	CCND1	P24385
CDC42	P60953	CFL1	P23528	CFLAR	O15519
CHUK	O15111	CREBBP	Q92793	CSF1R	P07333
CSK	P41240	CSNK1A1	P48729	CSNK1D	P48730
CSNK1E	P49674	CTNNB1	P35222	CYCS	P99999
DAAM1	Q9Y4D1	DKK1	O94907	DKK2	Q9UBU2
DKK4	Q9UBT3	DUSP1	P28562	DUSP6	Q16828
DVL1	O14640	DVL2	O14641, Q92997	DVL3	Q92997
EGFR	P00533	EGR1	P18146	EP300	Q09472
ERBB2	P04626	ERBB3	P21860-1	ERBB4	Q15303-1, Q15303-2
FGFR1	P11362-1, P11362-19	FGFR2	P21802-1, P21802-18, P21802-3, P21802-5	FGFR3	P22607-1, P22607-2
FGFR4	P22455	FLT1	P17948	FLT3	P36888
FLT4	P35916	FOS	P01100	FOXO1	Q12778
FOXO3	O43524	FOXO4	P98177	FZD1	Q9UP38
FZD10	Q9ULW2	FZD2	Q14332	FZD3	Q9NPG1
FZD4	Q9ULV1	FZD5	Q13467	FZD6	O60353
FZD7	O75084	FZD8	Q9H461	FZD9	O00144
GAB1	Q13480	GAB2	Q9UQC2	GRAP2	O75791
GRB2	P62993-1	GSK3A	P49840, P49841	GSK3B	P49841
IGF1R	P08069	IKBKB	O14920	IL6R	P08887, P08887-2
IL6ST	P40189-1	ILK	Q13418	IRAK1	P51617
IRS1	P35568	ITCH	Q96J02	JAK1	P23458
JAK2	O60674	JUN	P05412	KDR	P35968
KIT	P10721	KRAS	P01111, P01116	LEF1	Q9UJU2
LIF	P15018	LIFR	P42702	LIMK1	P53667
LIMK2	P53671	LRP5	O75197	LRP6	O75581
MAP2K1	Q02750	MAP2K2	P36507	MAP2K3	P46734
MAP2K4	P45985	MAP2K7	O14733	MAP3K11	Q16584
MAP3K5	Q99683	MAP3K7	O43318	MAP3K8	P41279
MAPK1	P28482	MAPK14	Q16539	MAPK3	P27361
MAPK8	P45983	MAPK9	P45984	MAPKAPK2	P49137
MDM2	Q00987	MET	P08581	MLST8	Q9BVC4
MMP2	P08253	MMP7	P08254	MMP9	P14780
MTOR	P42345	MYC	P01106	NFKB1	P19838

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
NFKB2	Q00653	NLK	Q9UBE8	PAK1	O75914, Q13153
PARD6A	Q9NPB6	PDGFRA	P16234	PDGFRB	P09619
PDPK1	O15530	PIAS1	O75925	PIK3CA	P42336
PLCG1	P19174	PLK1	P53350	PPM1A	P35813
PPP1CA	P62136	PRKACA	P17252	PRKCA	P17252
PRKCD	Q05655	PTEN	P60484	PTPN11	Q06124
PTPN6	P29350	RAC1	P63000	RAC2	P15153
RAC3	P60763	RAF1	P04049	REL	Q00653
RELA	Q04206	RELB	Q01201	RHEB	Q15382
RHOA	P61586	RICTOR	Q6R327	ROCK1	Q13464
RPS6KA1	Q15418	RPS6KA2	Q15349	RPS6KA3	P51812
RPS6KA4	O75676	RPS6KA5	O75582	RPS6KB1	P23443
RPS6KB2	Q9UBS0	RPTOR	Q8N122	SFRP1	Q8N474
SHC1	P29353-1, P29353-2, P29353-3	SKI	Q5VTY9	SKP2	Q13309
SMAD1	Q15797	SMAD2	Q15796	SMAD3	P84022
SMAD4	Q13485	SMAD5	Q99717	SMAD6	O43541
SMAD7	O15105	SMURF1	Q9HCE7	SMURF2	Q9HAU4
SOCS1	O15524	SOS1	Q07889	SRC	P12931
SRF	P11831	STAT1	P42224, P42224-1	STAT2	P52630
STAT3	P40763	SYK	P43405	TAB1	Q15750
TAB2	Q9NYJ8	TCF7	P36402	TCF7L1	Q9HCS4
TCF7L2	Q9NQB0	TGFB1	P01137	TGFBR1	P36897
TGFBR2	P37173	TIAM1	Q13009	TP53	P04637
TRAF6	Q9Y4K3	TSC1	Q92574	TSC2	P49815
VAV1	P15498				

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
AKT1	ENSG00000142208	AXIN1	ENSG00000103126	BAX	ENSG00000087088
BCL2	ENSG00000171791	CCND1	ENSG00000110092	CDC42	ENSG00000070831
CFL1	ENSG00000172757	CYCS	ENSG00000172115	DKK1	ENSG00000107984
EGFR	ENSG00000146648	EGR1	ENSG00000120738	ERBB2	ENSG00000141736
FLT4	ENSG00000037280	FOS	ENSG00000170345	FOXO1	ENSG00000150907
FOXO3	ENSG00000118689	GSK3A	ENSG00000105723	IL6R	ENSG00000160712
IRAK1	ENSG00000184216	ITCH	ENSG00000078747	KIT	ENSG00000157404
LIF	ENSG00000128342	LIFR	ENSG00000113594	MDM2	ENSG00000135679
MET	ENSG00000105976	MMP2	ENSG00000087245	MMP9	ENSG00000100985
MYC	ENSG00000136997	NLK	ENST00000407008	PLK1	ENSG00000166851
PTEN	ENSG00000171862, ENST00000371953	PTPN11	ENSG00000179295	PTPN6	ENSG00000111679
SHC1	ENSG00000160691	SMAD6	ENSG00000137834	SMAD7	ENSG00000101665
SMURF1	ENSG00000198742	SOCS1	ENSG00000185338	STAT1	ENSG00000115415
STAT3	ENSG00000168610	TGFB1	ENSG00000105329	TP53	ENSG00000141510

7. Identifiers not found

These 7 identifiers were not found neither mapped to any entity in Reactome.

ACVR1

CFL2

DKK3

MAP3K4

MAPK8IP3

MXD1

RND3