

Pathway Analysis Report

GBM Uniprot

This report contains the pathway analysis results for the submitted sample 'GBM Uniprot'. Analysis was performed against Reactome version 63 using any resource identifiers for the mapping. The web link to these results is:

<https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAxODAyMTIxMTI5MzdfMQ\%3D\%3D>

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

Contents

1	Introduction	2
2	Pathway details	3
2.1	Diseases of signal transduction (R-HSA-5663202)	3
2.2	Signaling by Receptor Tyrosine Kinases (R-HSA-9006934)	4
2.3	PI3K/AKT Signaling in Cancer (R-HSA-2219528)	5
2.4	Signal Transduction (R-HSA-162582)	7
2.5	Intracellular signaling by second messengers (R-HSA-9006925)	9
2.6	PIP3 activates AKT signaling (R-HSA-1257604)	10
2.7	Negative regulation of the PI3K/AKT network (R-HSA-199418)	11
2.8	PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling (R-HSA-6811558)	12
2.9	Signaling by FGFR in disease (R-HSA-1226099)	14
2.10	Disease (R-HSA-1643685)	16
2.11	Signaling by SCF-KIT (R-HSA-1433557)	17
2.12	Constitutive Signaling by Aberrant PI3K in Cancer (R-HSA-2219530)	18
2.13	Signaling by VEGF (R-HSA-194138)	19
2.14	VEGFA-VEGFR2 Pathway (R-HSA-4420097)	20
2.15	Insulin receptor signalling cascade (R-HSA-74751)	21
2.16	Signaling by PDGF (R-HSA-186797)	22
2.17	Signaling by Insulin receptor (R-HSA-74752)	23
2.18	IRS-mediated signalling (R-HSA-112399)	24
2.19	MAPK1/MAPK3 signaling (R-HSA-5684996)	25
2.20	Downstream signal transduction (R-HSA-186763)	26
2.21	IRS-related events triggered by IGF1R (R-HSA-2428928)	27
2.22	Signaling by FGFR1 in disease (R-HSA-5655302)	28
2.23	IGF1R signaling cascade (R-HSA-2428924)	30
2.24	RAF/MAP kinase cascade (R-HSA-5673001)	31
2.25	Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R) (R-HSA-2404192)	32

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. Inferred orthologous reactions 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.

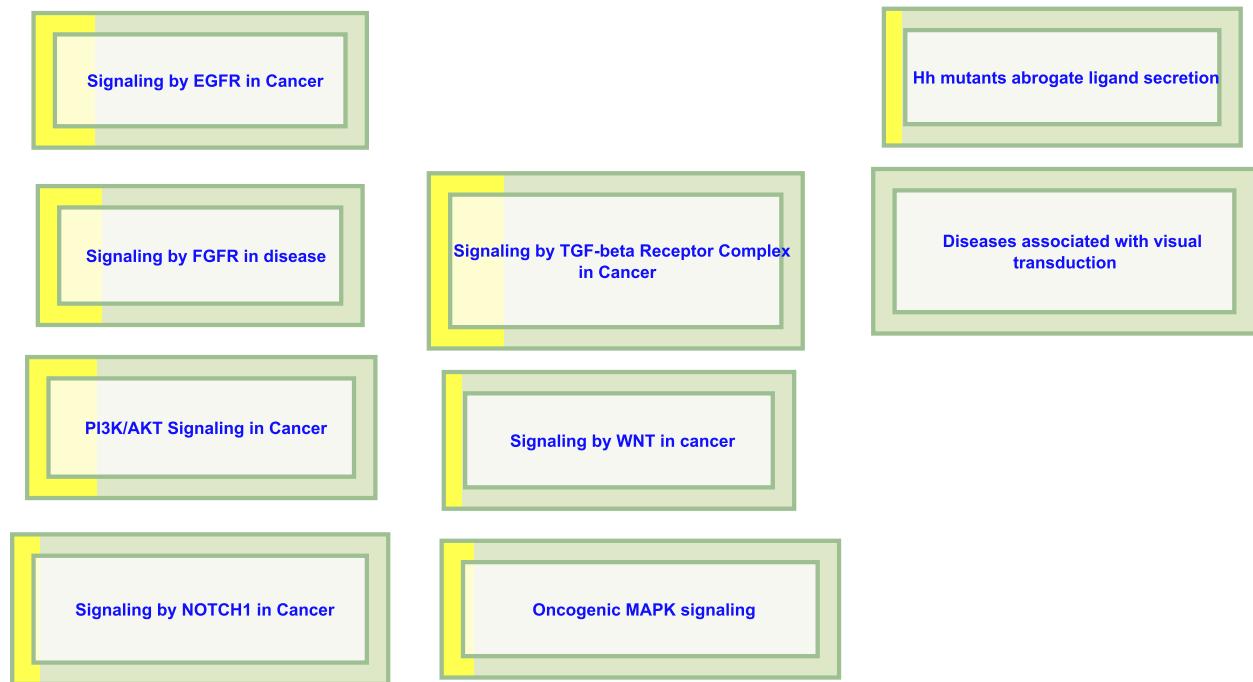
Reactome's annotated data describe reactions possible if all annotated proteins and small molecules were present and active simultaneously in a cell. By overlaying an experimental dataset on these annotations, a user can perform a pathway over-representation analysis. By overlaying quantitative expression 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 (BenjaminiHochberg 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:

- The Reactome pathway Knowledgebase. Nucleic Acids Research, Volume 44, Issue D1,4 January 2016, Pages D481D487
- Reactome pathway analysis: a high-performance in-memory approach. BMC Bioinformatics, 18, 142, 2 March 2017

2 Pathway details

2.1 Diseases of signal transduction (R-HSA-5663202)



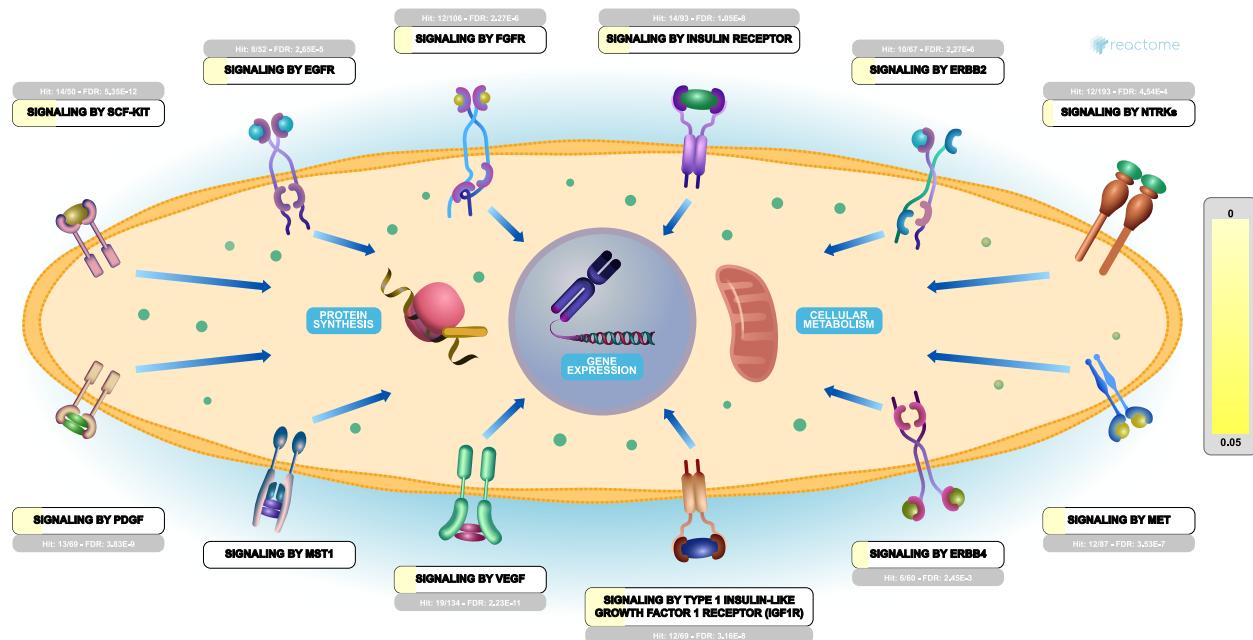
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Signaling processes are central to human physiology (e.g., Pires-da Silva & Sommer 2003), and their disruption by either germ-line and somatic mutation can lead to serious disease. Here, the molecular consequences of mutations affecting visual signal transduction and signaling by diverse growth factors are annotated.

References

- Pires-daSilva Andr, Sommer Ralf J, The evolution of signalling pathways in animal development, Nat. Rev. Genet., 4, 2003, 39-49, 12509752.

2.2 Signaling by Receptor Tyrosine Kinases (R-HSA-9006934)

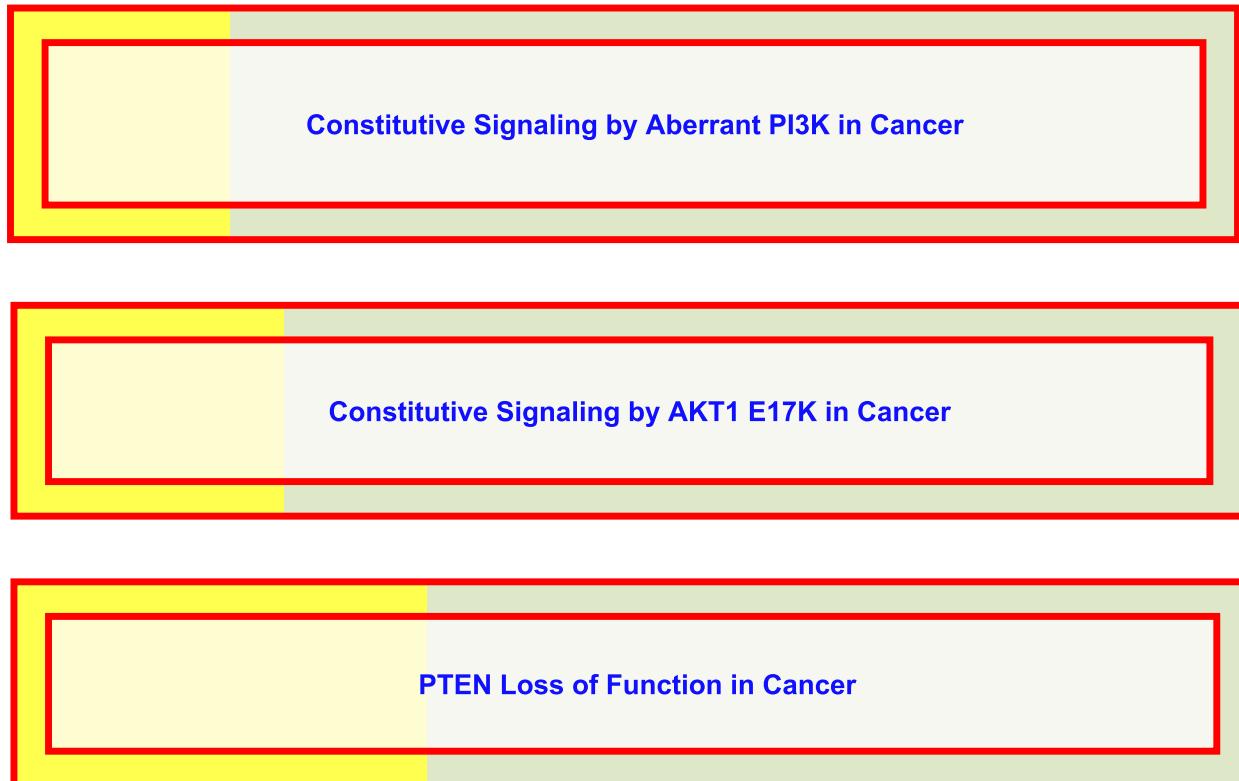


Receptor tyrosine kinases (RTKs) are a major class of cell surface proteins involved in Signal Transduction. Human cells contain ~60 RTKs, grouped into 20 subfamilies based on their domain architecture. All RTK subfamilies are characterized by an extracellular ligand-binding domain, a single transmembrane 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 (reviewed 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.

References

- Lemmon Mark A, Schlessinger Joseph, Cell signaling by receptor tyrosine kinases, *Cell*, 141, 2010, 1117-34, 20602996.
- McKay, Morrison Deborah K, Integrating signals from RTKs to ERK/MAPK, *Oncogene*, 26, 2007, 3113-21, 17496910.
- Wellbrock Claudia, Karasarides Maria, Marais Richard, The RAF proteins take centre stage, *Nat Rev Mol Cell Biol*, 5, 2004, 875-85, 15520807.
- Manning, Cantley Lewis C, AKT/PKB signaling: navigating downstream, *Cell*, 129, 2007, 1261-74, 17604717.
- Patterson Randen L, van Rossum Damian B, Nikolaidis, Gill Donald L, Snyder, Phospholipase C-gamma: diverse roles in receptor-mediated calcium signaling, *Trends Biochem Sci*, 30, 2005, 688-97, 16260143.

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



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).

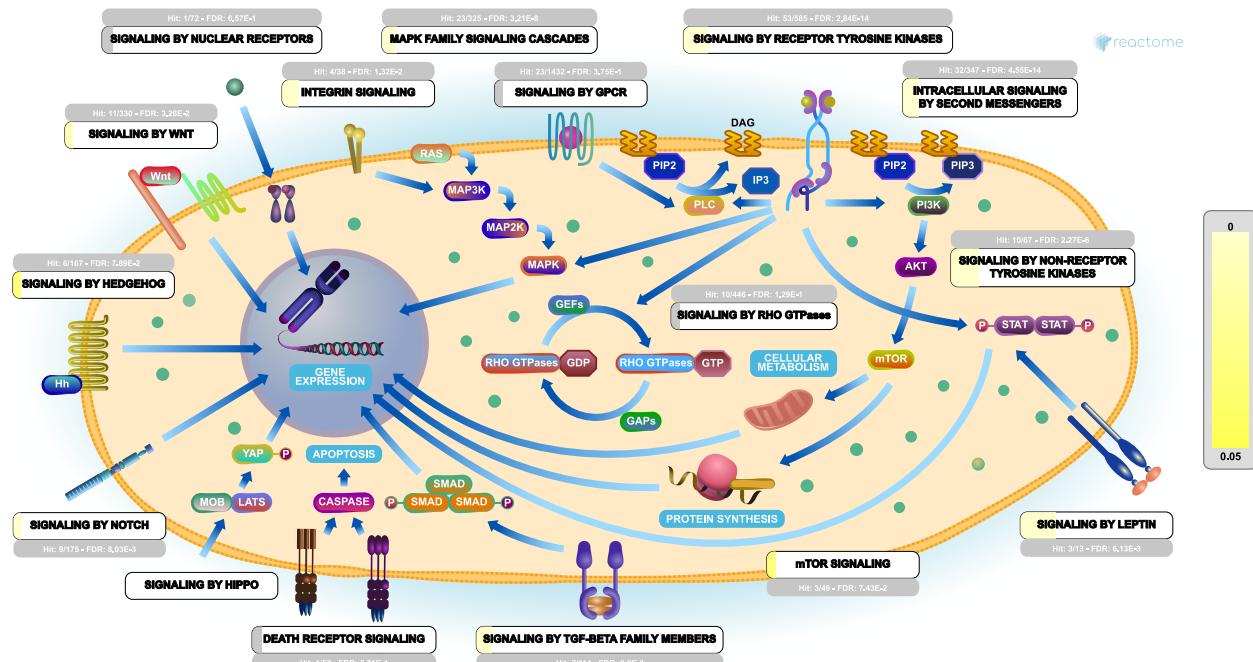
Loss-of-function mutations affecting the phosphatase domain of PTEN are frequently found in sporadic cancers (Kong et al. 1997, Lee et al. 1999, Han et al. 2000), as well as in PTEN hamartoma tumor syndromes (PHTS) (Marsh et al. 1998). PTEN can also be inactivated by gene deletion or epigenetic silencing, 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, Cantley Lewis C, AKT/PKB signaling: navigating downstream, *Cell*, 129, 2007, 1261-74, 17604717.
- Liu Pixu, Cheng Hailing, Roberts Thomas M, Zhao Jean J, Targeting the phosphoinositide 3-kinase pathway in cancer, *Nat Rev Drug Discov*, 8, 2009, 627-44, 19644473.
- Hollander M Christine, Blumenthal Gideon M, Dennis Phillip A, PTEN loss in the continuum of common cancers, rare syndromes and mouse models, *Nat. Rev. Cancer*, 11, 2011, 289-301, 21430697.
- Huang Chuan-Hsiang, Mandelker Diana, Schmidt-Kittler Oleg, Samuels Yardena, Velculescu Victor E et al., The structure of a human p110alpha/p85alpha complex elucidates the effects of oncogenic PI3Kalpha mutations, *Science*, 318, 2007, 1744-8, 18079394.
- Zhao Jean J, Liu Zhenning, Wang Li, Shin Eyoung, Loda Massimo F et al., The oncogenic properties of mutant p110alpha and p110beta phosphatidylinositol 3-kinases in human mammary epithelial cells, *Proc. Natl. Acad. Sci. U.S.A.*, 102, 2005, 18443-8, 16339315.

2.4 Signal Transduction (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 subunits. 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).

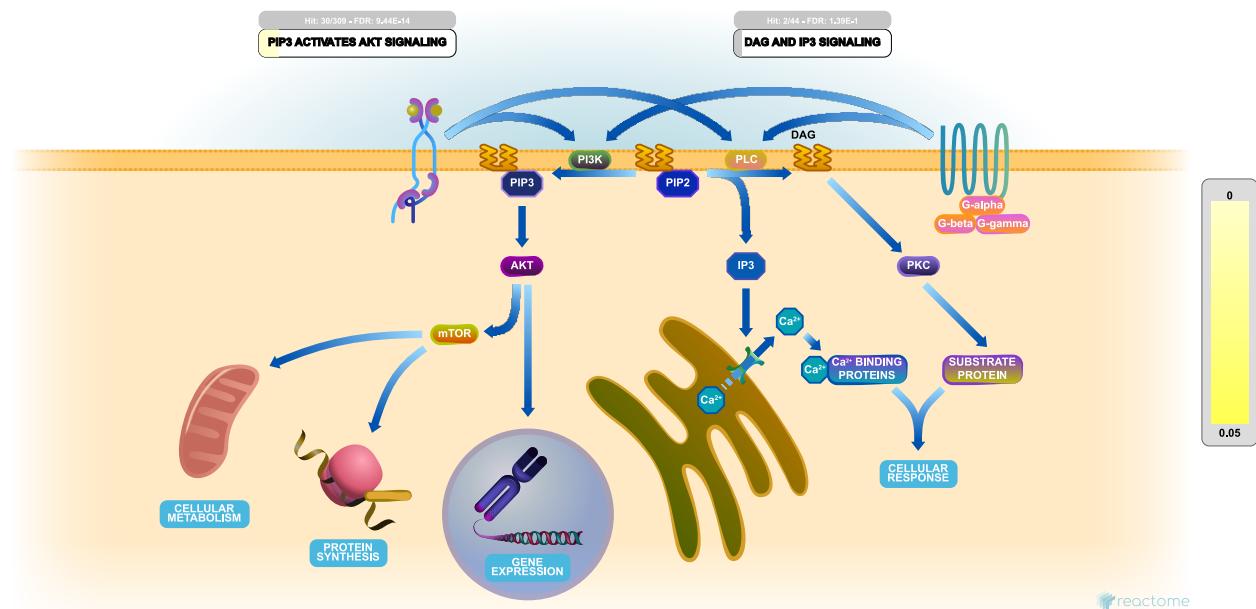
Integrins are activated by extracellular matrix components, such as fibronectin and collagen, leading to conformational change and clustering of integrins on the cell surface. This results in activation of integrin-linked kinase and other cytosolic kinases and, in co-operation with RTK signaling, regulates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

References

- Manning, Cantley Lewis C, AKT/PKB signaling: navigating downstream, *Cell*, 129, 2007, 1261-74, 17604717.
- Kopan Raphael, Ilagan Ma Xenia, The canonical Notch signaling pathway: unfolding the activation mechanism, *Cell*, 137, 2009, 216-33, 19379690.
- Kang, Liu Cheng, Derynck, New regulatory mechanisms of TGF-beta receptor function, *Trends Cell Biol*, 19, 2009, 385-94, 19648010.
- Miyazono Kohei, Kamiya Yuto, Morikawa Masato, Bone morphogenetic protein receptors and signal transduction, *J Biochem*, 147, 2010, 35-51, 19762341.
- Avraham Roi, Yarden Yosef, Feedback regulation of EGFR signalling: decision making by early and delayed loops, *Nat Rev Mol Cell Biol*, 12, 2011, 104-17, 21252999.

2.5 Intracellular signaling by second messengers ([R-HSA-9006925](#))

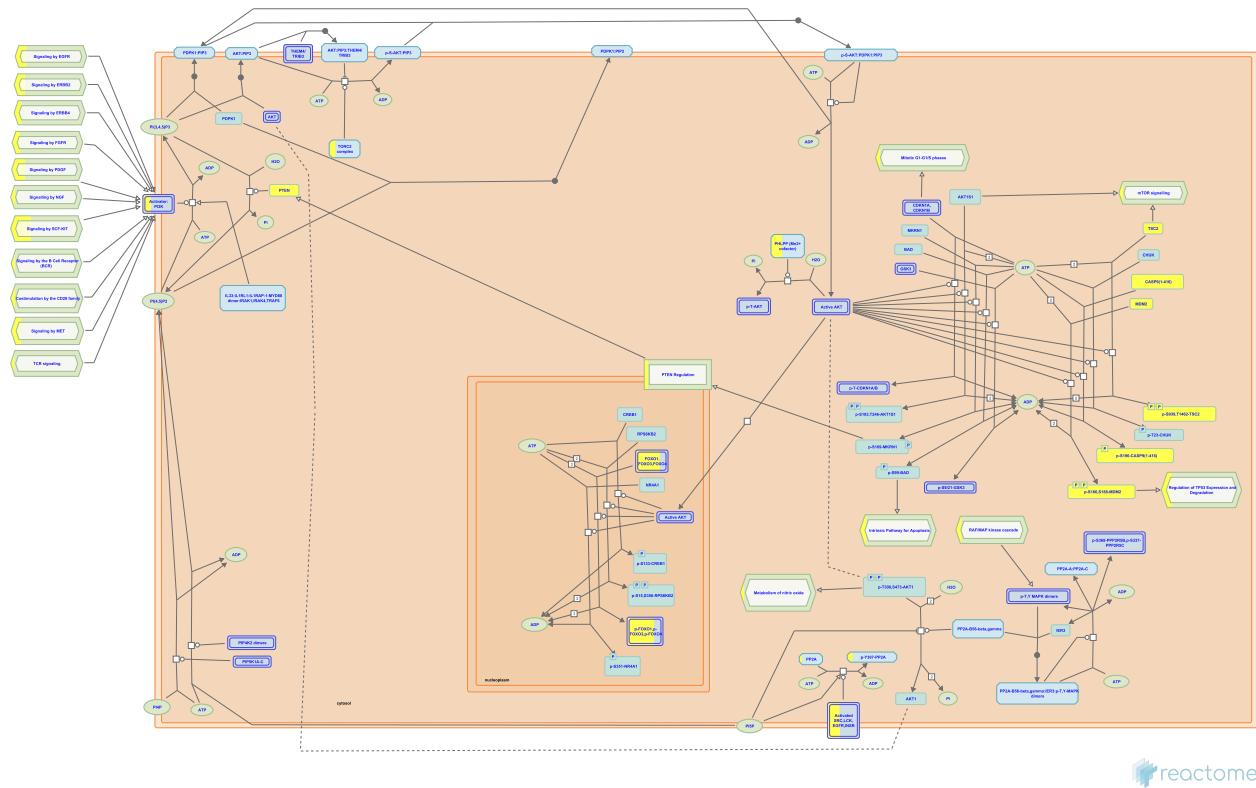


Second messengers are generated within the cell as a downstream step in signal transduction cascades initiated by the interaction of an external stimulus with a cell surface receptor. Common second messengers include DAG, cAMP, cGMP, IP3, Ca²⁺ and phosphatidylinositols (reviewed in Kang et al, 2015;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

References

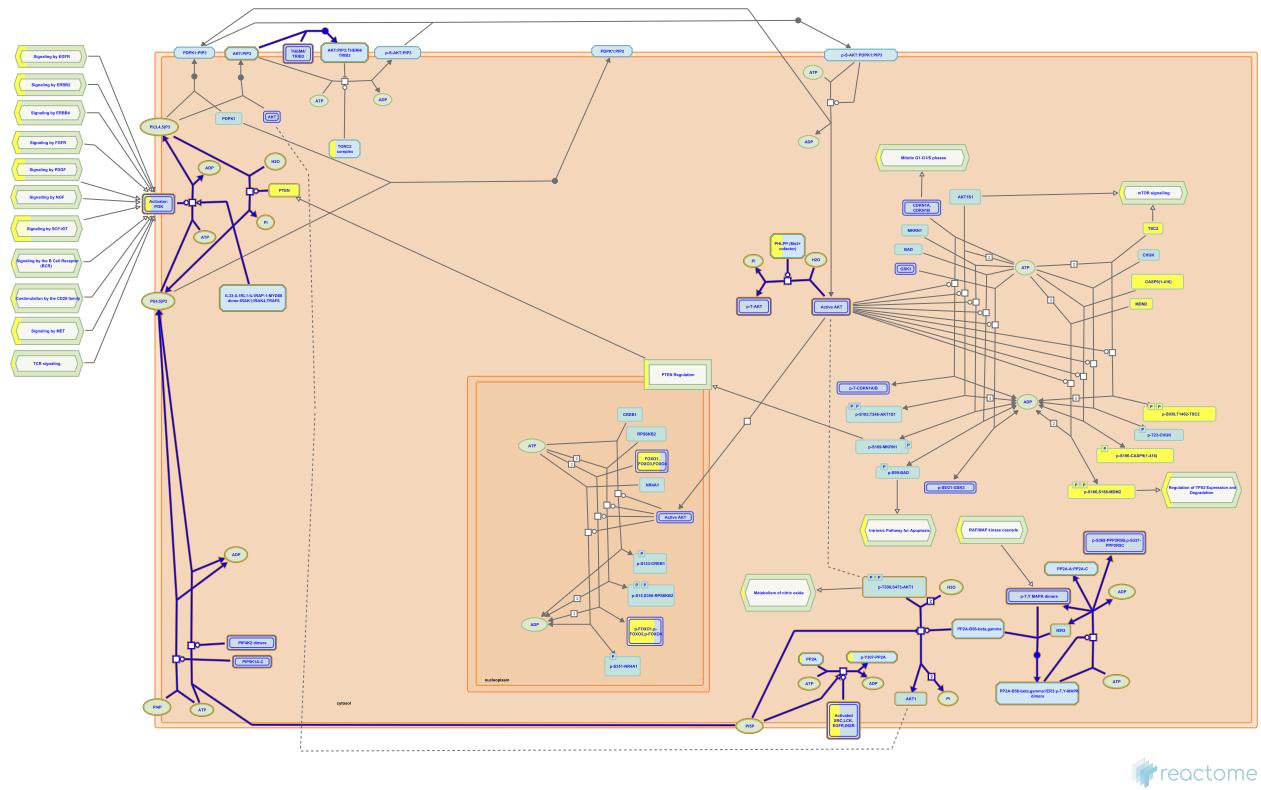
- Ahmad F, Murata T, Shimizu K, Degerman E, Maurice D et al., Cyclic nucleotide phosphodiesterases: important signaling modulators and therapeutic targets, *Oral Dis*, 21, 2015, e25-50, 25056711.
- Raker Verena Katharina, Becker Christian, Steinbrink Kerstin, The cAMP Pathway as Therapeutic Target in Autoimmune and Inflammatory Diseases, *Front Immunol*, 7, 2016, 123, 27065076.
- Pinto Mauro Cunha Xavier, Kihara Alexandre Hiroaki, Goulart Vnia A M, Tonelli Fernanda M P, Gomes Katia N et al., Calcium signaling and cell proliferation, *Cell. Signal.*, 27, 2015, 2139-49, 26275497.
- Kang Du-Seock, Yang Yong Ryoul, Lee Cheol, Kim SaetByeol, Ryu Sung Ho et al., Roles of phosphoinositide-specific phospholipase C1 in brain development, *Adv Biol Regul*, 60, 2016, 167-73, 26588873.
- Levine Tim P, Patel Sandip, Signalling at membrane contact sites: two membranes come together to handle second messengers, *Curr. Opin. Cell Biol.*, 39, 2016, 77-83, 26922871.

2.6 PIP3 activates AKT signaling (R-HSA-1257604)



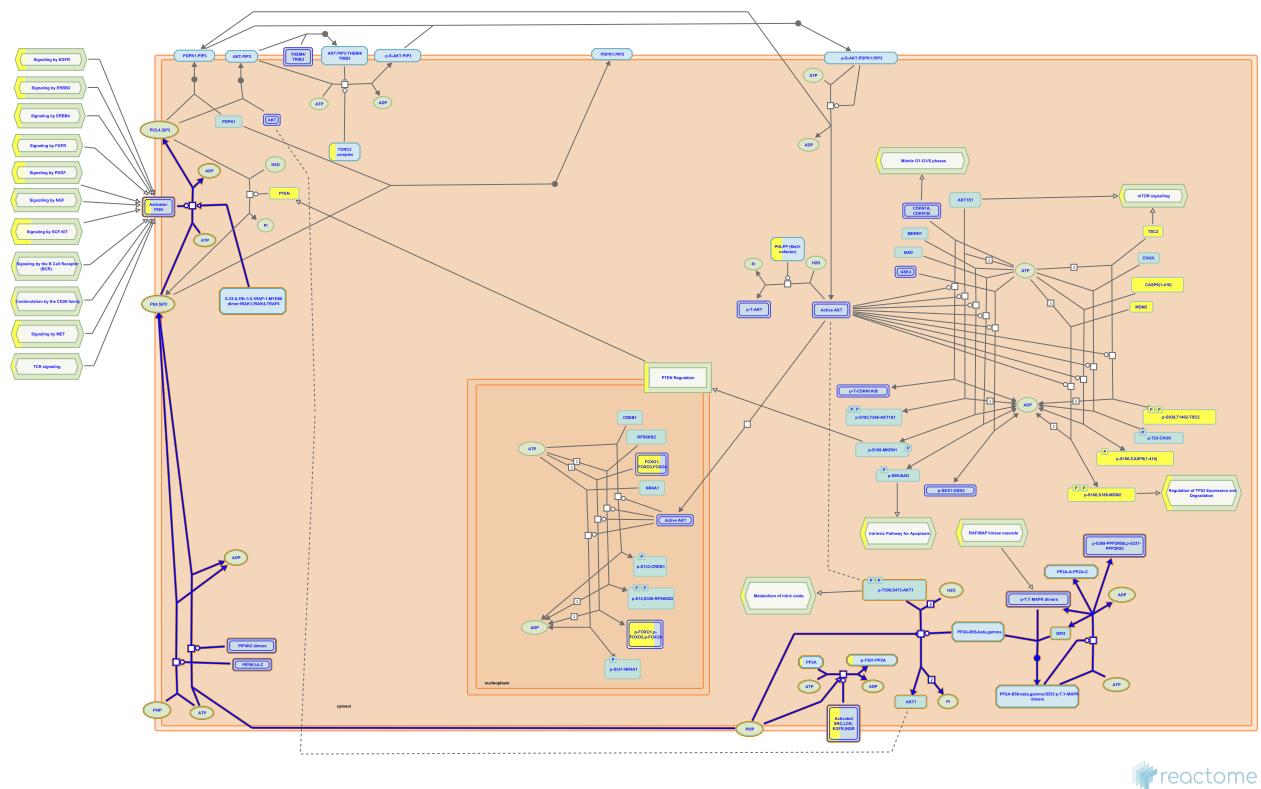
Signaling by AKT is one of the key outcomes of receptor tyrosine kinase (RTK) activation. AKT is activated by the cellular second messenger PIP3, a phospholipid that is generated by PI3K. In unstimulated cells, PI3K class IA enzymes reside in the cytosol as inactive heterodimers composed of p85 regulatory 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.

2.7 Negative regulation of the PI3K/AKT network (R-HSA-199418)



The PI3K/AKT network is negatively regulated by phosphatases that dephosphorylate PIP3, thus hampering AKT activation.

2.8 PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling (R-HSA-6811558)



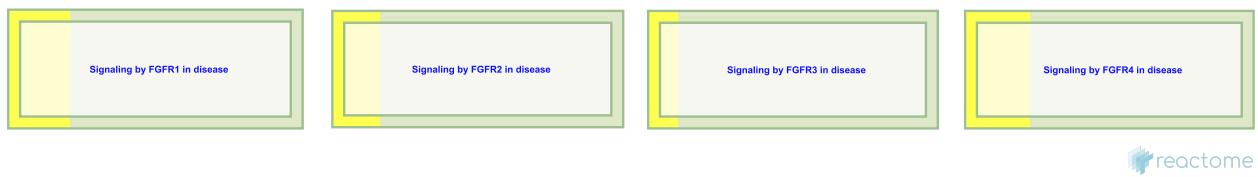
Phosphatidylinositol-5-phosphate (PI5P) may modulate PI3K/AKT signaling in several ways. PI5P is used as a substrate for production of phosphatidylinositol-4,5-bisphosphate, PI(4,5)P₂ (Rameh et al. 1997, Clarke et al. 2008, Clarke et al. 2010, Clarke and Irvine 2013, Clarke et al. 2015), which serves as a substrate for activated PI3K, resulting in the production of PIP₃ (Mandelker et al. 2009, Burke et al. 2011). The majority of PI(4,5)P₂ in the cell, however, is produced from the phosphatidylinositol-4-phosphate (PI4P) substrate (Zhang et al. 1997, Di Paolo et al. 2002, Oude Weernink et al. 2004, Halstead et al. 2006, Oude Weernink et al. 2007). PIP₃ is necessary for the activating phosphorylation of AKT. AKT1 can be deactivated by the protein phosphatase 2A (PP2A) complex that contains a regulatory subunit B56-beta (PPP2R5B) or B56-gamma (PPP2R5C). PI5P inhibits AKT1 dephosphorylation by PP2A through an unknown mechanism (Ramel et al. 2009). Increased PI5P levels correlate with inhibitory phosphorylation(s) of the PP2A complex. MAPK1 (ERK2) and MAPK3 (ERK1) are involved in inhibitory phosphorylation of PP2A, in a process that involves IER3 (IEX-1) (Letourneux et al. 2006, Rocher et al. 2007). It is uncertain, however, whether PI5P is in any way involved in ERK-mediated phosphorylation of PP2A or if it regulates another PP2A kinase.

References

- Rameh Lucia, Tolias, Duckworth, Cantley Lewis C, A new pathway for synthesis of phosphatidylinositol-4,5-bisphosphate, *Nature*, 390, 1997, 192-6, 9367159.
- Clarke, Emson, Irvine, Localization of phosphatidylinositol phosphate kinase IIgamma in kidney to a membrane trafficking compartment within specialized cells of the nephron, *Am J Physiol Renal Physiol*, 295, 2008, F1422-30, 18753295.
- Clarke, Wang, Irvine, Localization, regulation and function of type II phosphatidylinositol 5-phosphate 4-kinases, *Adv Enzyme Regul*, 50, 2010, 12-8, 19896968.
- Clarke Jonathan H, Irvine Robin F, Evolutionarily conserved structural changes in phosphatidylinositol 5-phosphate 4-kinase (PI5P4K) isoforms are responsible for differences in enzyme activity and localization, *Biochem. J.*, 454, 2013, 49-57, 23758345.

- Clarke Jonathan H, Giudici Maria-Luisa, Burke John E, Williams Roger L, Maloney David J et al., The function of phosphatidylinositol 5-phosphate 4-kinase (PI5P4K) explored using a specific inhibitor that targets the PI5P-binding site, *Biochem. J.*, 466, 2015, 359-67, 25495341.

2.9 Signaling by FGFR in disease (R-HSA-1226099)



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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).

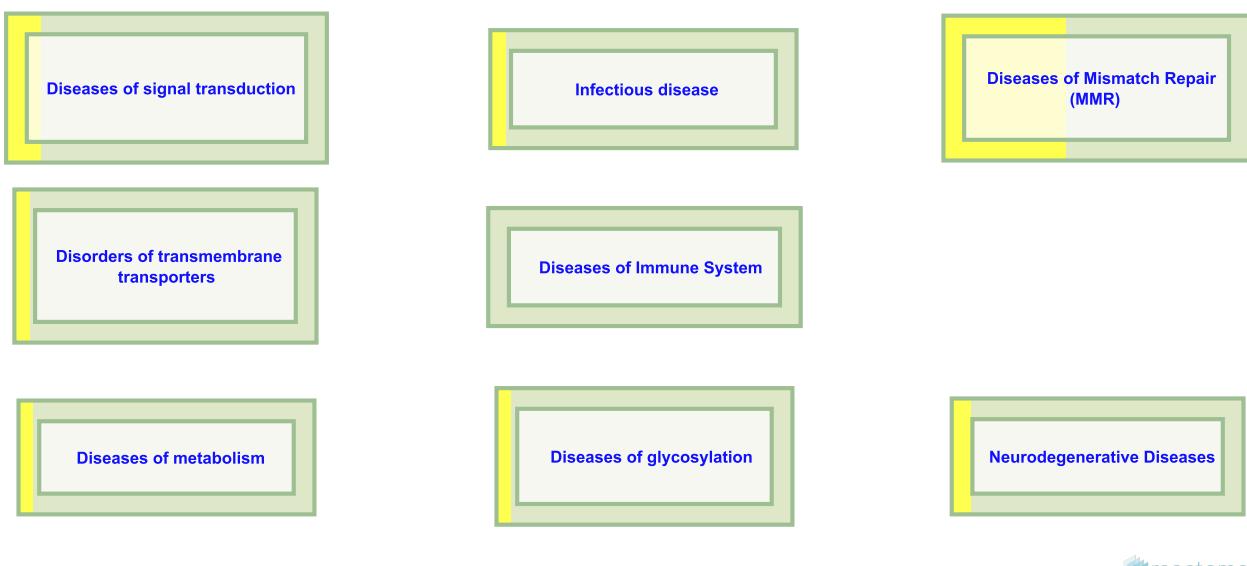
In addition to activating point mutations, the FGFR1, 2 and 3 genes are subject to misregulation in cancer through gene amplification and translocation events, which are thought to lead to overexpression and ligand-independent dimerization (Weiss, 2010; Turner, 2010; Kunii, 2008; Takeda, 2007; Chesi, 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 Melanie K, Donoghue Daniel J, FGFR activation in skeletal disorders: too much of a good thing, Trends Genet, 13, 1997, 178-82, 9154000.

- Burke David, Wilkes David, Blundell Tom L, Malcolm Sue, Fibroblast growth factor receptors: lessons from the genes, *Trends Biochem Sci*, 23, 1998, 59-62, 9538690.
- Cunningham Michael L, Seto Marianne L, Ratisoontorn Chootima, Heike Carrie L, Hing Anne V, Syndromic craniosynostosis: from history to hydrogen bonds, *Orthod Craniofac Res*, 10, 2007, 67-81, 17552943.
- Harada Daisuke, Yamanaka Yoshitaka, Ueda Koso, Tanaka Hiroyuki, Seino Yoshiki, FGFR3-related dwarfism and cell signaling, *J Bone Miner Metab*, 27, 2009, 9-15, 19066716.
- Galvin Brendan D, Hart Kristen C, Meyer April N, Webster Melanie K, Donoghue Daniel J, 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, 1996, 7894-9, 8755573.

2.10 Disease ([R-HSA-1643685](#))



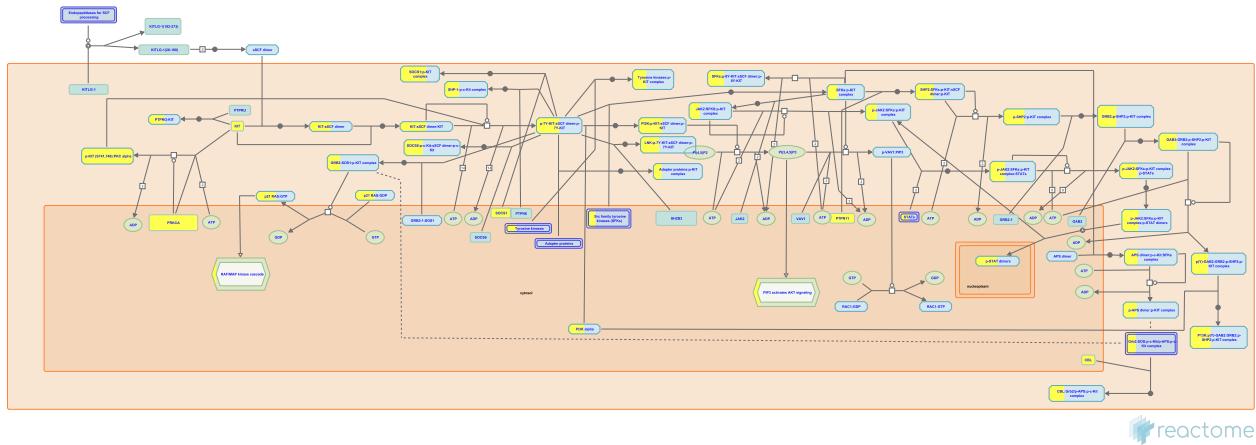
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Biological processes are captured in Reactome by identifying the molecules (DNA, RNA, protein, small molecules) involved in them and describing the details of their interactions. From this molecular viewpoint, human disease pathways have three mechanistic causes: the inclusion of microbially-expressed proteins, altered functions of human proteins, or changed expression levels of otherwise functionally normal human proteins.

The first group encompasses the infectious diseases such as influenza, tuberculosis and HIV infection. The second group involves human proteins modified either by a mutation or by an abnormal post-translational event that produces an aberrant protein with a novel function. Examples include somatic mutations of EGFR and FGFR (epidermal and fibroblast growth factor receptor) genes, which encode constitutively active receptors that signal even in the absence of their ligands, or the somatic mutation of IDH1 (isocitrate dehydrogenase 1) that leads to an enzyme active on 2-oxoglutarate rather than isocitrate, or the abnormal protein aggregations of amyloidosis which lead to diseases such as Alzheimer's.

Infectious diseases are represented in Reactome as microbial-human protein interactions and the consequent events. The existence of variant proteins and their association with disease-specific biological processes is represented by inclusion of the modified protein in a new or variant reaction, an extension to the 'normal' pathway. Diseases which result from proteins performing their normal functions but at abnormal rates can also be captured, though less directly. Many mutant alleles encode proteins that retain their normal functions but have abnormal stabilities or catalytic efficiencies, leading to normal reactions that proceed to abnormal extents. The phenotypes of such diseases can be revealed when pathway annotations are combined with expression or rate data from other sources.

2.11 Signaling by SCF-KIT (R-HSA-1433557)

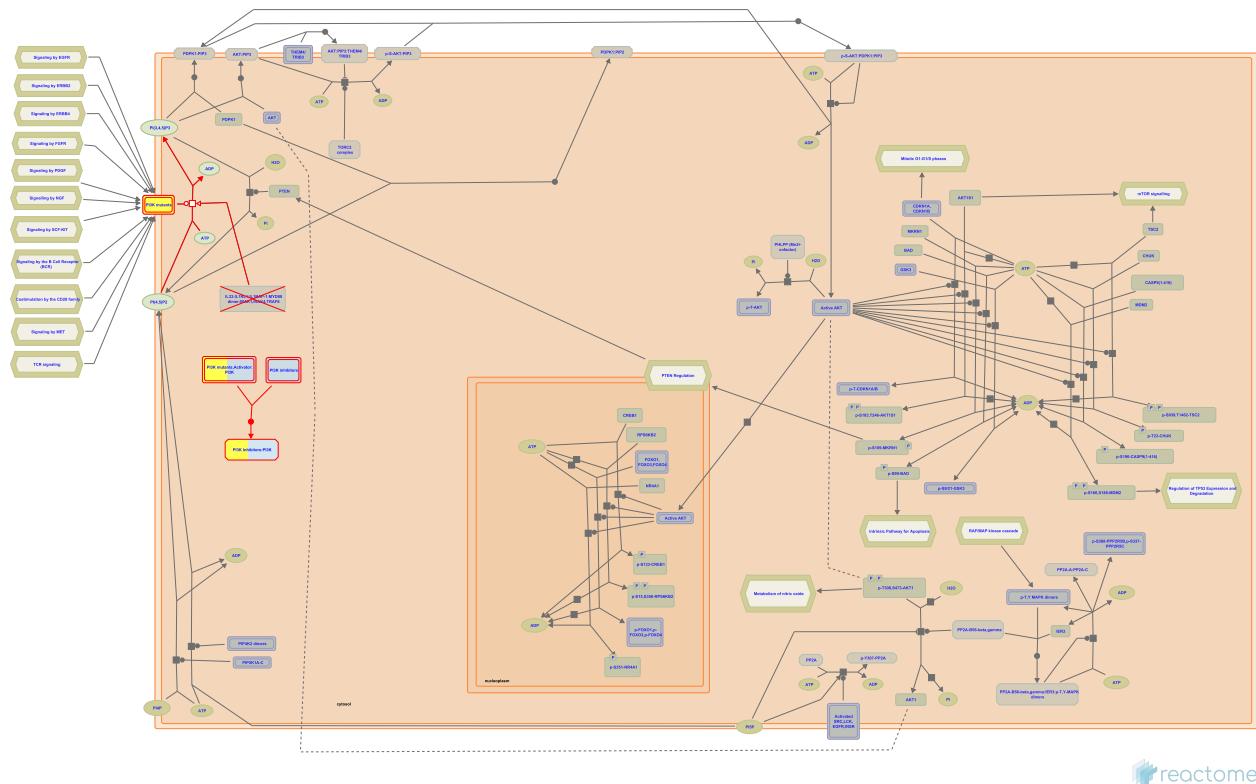


Stem cell factor (SCF) is a growth factor with membrane bound and soluble forms. It is expressed by fibroblasts and endothelial cells throughout the body, promoting proliferation, migration, survival and differentiation of hematopoietic progenitors, melanocytes and germ cells.(Linnekin 1999, Ronnstrand 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, Hallberg, c-Kit—a hematopoietic cell essential receptor tyrosine kinase, Int J Biochem Cell Biol, 39, 2007, 1995-8, 17350321.
- Ronnstrand Lars, Signal transduction via the stem cell factor receptor/c-Kit, Cell Mol Life Sci, 61, 2004, 2535-48, 15526160.
- Reber, Da Silva, Frossard, Stem cell factor and its receptor c-Kit as targets for inflammatory diseases, Eur J Pharmacol, 533, 2006, 327-40, 16483568.
- Lennartsson, Ronnstrand Lars, The stem cell factor receptor/c-Kit as a drug target in cancer, Curr Cancer Drug Targets, 6, 2006, 65-75, 16475976.
- Masson, Ronnstrand Lars, Oncogenic signaling from the hematopoietic growth factor receptors c-Kit and Flt3, Cell Signal, 21, 2009, 1717-26, 19540337.

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



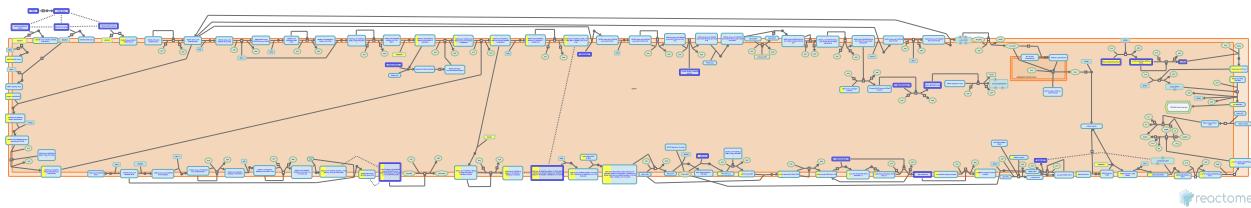
Diseases: cancer.

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 Chuan-Hsiang, Mandelker Diana, Schmidt-Kittler Oleg, Samuels Yardena, Velculescu Victor E et al., The structure of a human p110alpha/p85alpha complex elucidates the effects of oncogenic PI3Kalpha mutations, *Science*, 318, 2007, 1744-8, 18079394.
- Zhao Jean J, Liu Zhenning, Wang Li, Shin Eyoung, Loda Massimo F et al., The oncogenic properties of mutant p110alpha and p110beta phosphatidylinositol 3-kinases in human mammary epithelial cells, *Proc. Natl. Acad. Sci. U.S.A.*, 102, 2005, 18443-8, 16339315.
- Miled Nabil, Yan Ying, Hon Wai-Ching, Perisic Olga, Zvelebil Marketa et al., Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit, *Science*, 317, 2007, 239-42, 17626883.
- Horn S, Bergholz U, Jcker M, McCubrey J A, Trumper L et al., Mutations in the catalytic subunit of class IA PI3K confer leukemogenic potential to hematopoietic cells, *Oncogene*, 27, 2008, 4096-106, 18317450.
- Sun Minghao, Hillmann Petra, Hofmann Bianca T, Hart Jonathan R, Vogt Peter K, 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, 2010, 15547-52, 20713702.

2.13 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).

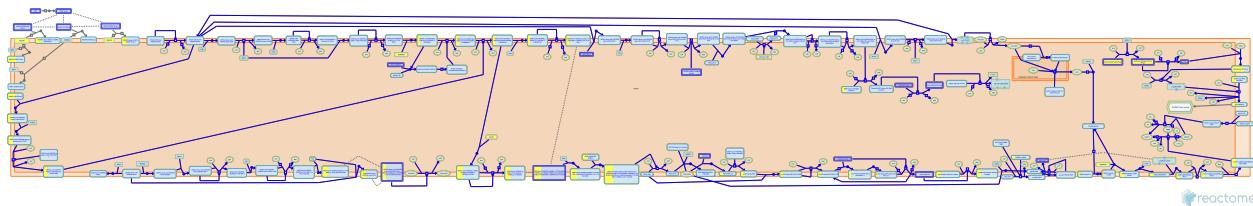
Molecular features of the VEGF signaling cascades are outlined in the figure below (from Olsson et al. 2006; Nature Publishing Group). Tyrosine residues in the intracellular domains of VEGF receptors 1, 2, and 3 are indicated by dark blue boxes; residues susceptible to phosphorylation are numbered. A 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; PLCgamma, 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. Details of signaling events and their biological outcome, concisely illustrated in the image below, will be available in future versions of this pathway.

References

- Shibuya, Claesson-Welsh Lena, Signal transduction by VEGF receptors in regulation of angiogenesis and lymphangiogenesis, *Exp Cell Res*, 312, 2006, 549-60, 16336962.
- Hicklin, Ellis, Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis, *J Clin Oncol*, 23, 2005, 1011-27, 15585754.
- Cross, Dixielius, Matsumoto T, Claesson-Welsh Lena, VEGF-receptor signal transduction, *Trends Biochem Sci*, 28, 2003, 488-94, 13678960.
- Matsumoto T, Mugishima, Signal transduction via vascular endothelial growth factor (VEGF) receptors and their roles in atherogenesis, *J Atheroscler Thromb*, 13, 2006, 130-5, 16835467.

2.14 VEGFA-VEGFR2 Pathway (R-HSA-4420097)



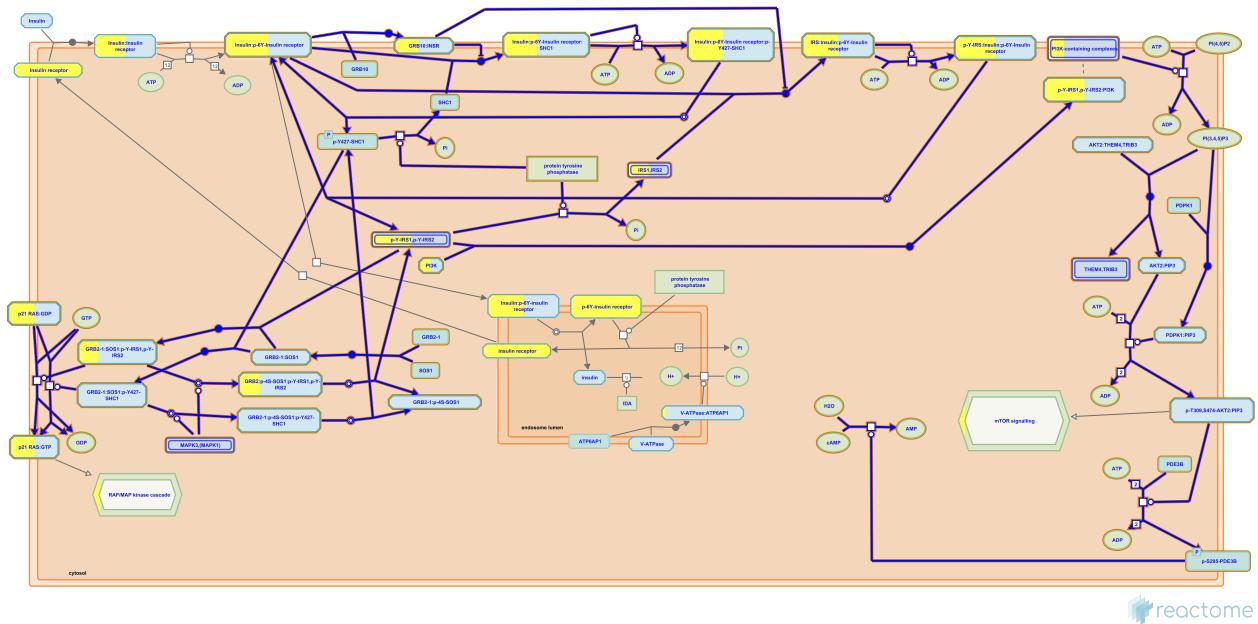
Cellular compartments: plasma membrane.

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, Dimberg, Kreuger, Claesson-Welsh Lena, VEGF receptor signalling - in control of vascular function, Nat Rev Mol Cell Biol, 7, 2006, 359-71, 16633338.
- Cross, Dixielius, Matsumoto T, Claesson-Welsh Lena, VEGF-receptor signal transduction, Trends Biochem Sci, 28, 2003, 488-94, 13678960.
- Lohela Marja, Bry Maija, Tammela Tuomas, Alitalo Kari, VEGFs and receptors involved in angiogenesis versus lymphangiogenesis, Curr. Opin. Cell Biol., 21, 2009, 154-65, 19230644.
- Otrack Zaher K, Makarem Jawad A, Shamseddine Ali I, Vascular endothelial growth factor family of ligands and receptors: review, Blood Cells Mol. Dis., 38, 2007, 258-68, 17344076.

2.15 Insulin receptor signalling cascade (R-HSA-74751)



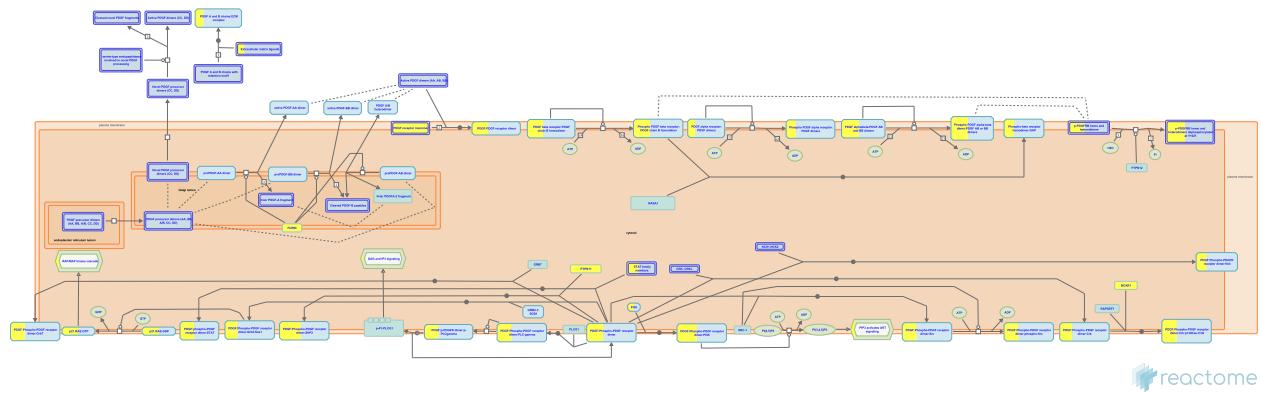
Cellular compartments: cytosol.

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 downregulates its signalling activity.

References

- Bevan P, Insulin signalling., J Cell Sci, 114, 2001, 1429-30, 11282018.
- Shepherd P R, Withers D J, Siddle K, Phosphoinositide 3-kinase: the key switch mechanism in insulin signalling., Biochem J, 333, 1998, 471-90, 9677303.

2.16 Signaling by PDGF (R-HSA-186797)

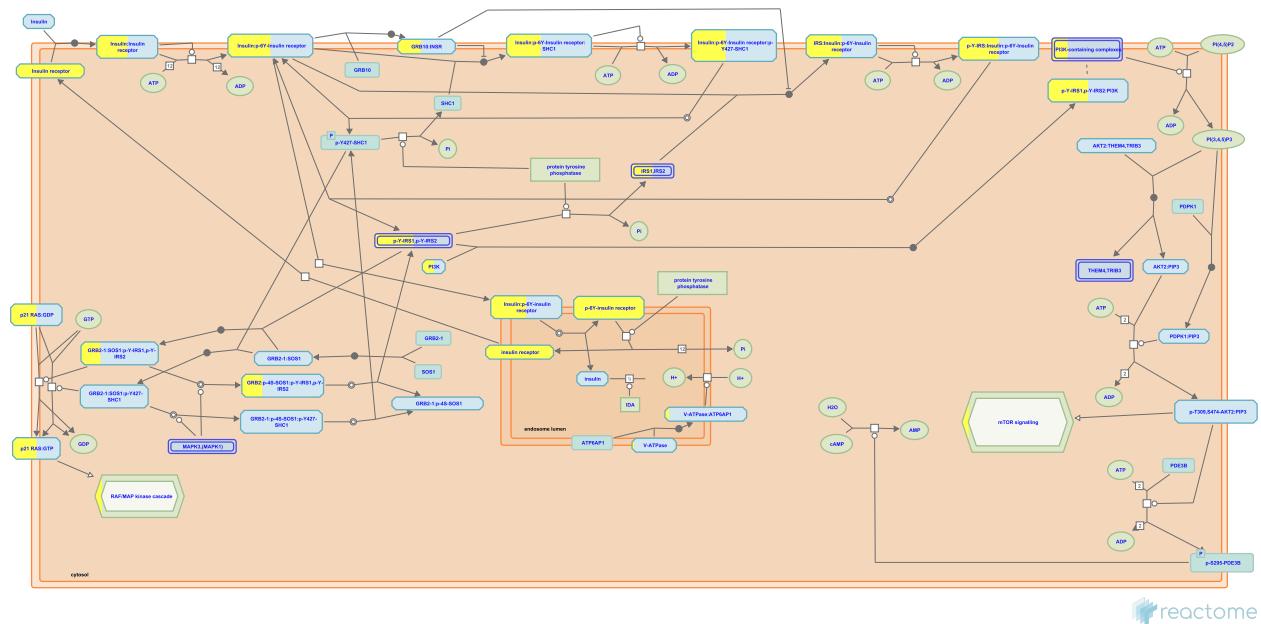


Platelet-derived Growth Factor (PDGF) is a potent stimulator of growth and motility of connective tissue cells such as fibroblasts and smooth muscle cells as well as other cells such as capillary endothelial cells and neurons. The PDGF family of growth factors is composed of four different polypeptide chains encoded by four different genes. The classical PDGF chains, PDGF-A and PDGF-B, and more recently discovered PDGF-C and PDGF-D. The four PDGF chains assemble into disulphide-bonded dimers via homo- or heterodimerization, and five different dimeric isoforms have been described so far; PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and PDGF-DD. It is notable that no heterodimers involving PDGF-C and PDGF-D chains have been described. PDGF exerts its effects by binding to, and activating, two protein tyrosine kinase (PTK) receptors, alpha and beta. These receptors dimerize and undergo autophosphorylation. The phosphorylation sites then attract downstream effectors to transduct the signal into the cell.

References

- Heldin Carl-Henrik, Westermark, Mechanism of action and in vivo role of platelet-derived growth factor, *Physiol Rev*, 79, 1999, 1283-316, 10508235.
- Heldin Carl-Henrik, Ostman, Rnnstrand, Signal transduction via platelet-derived growth factor receptors, *Biochim Biophys Acta*, 1378, 1998, F79-113, 9739761.
- Fredriksson, Li Hao, Eriksson, The PDGF family: four gene products form five dimeric isoforms, *Cytokine Growth Factor Rev*, 15, 2004, 197-204, 15207811.

2.17 Signaling by Insulin receptor (R-HSA-74752)



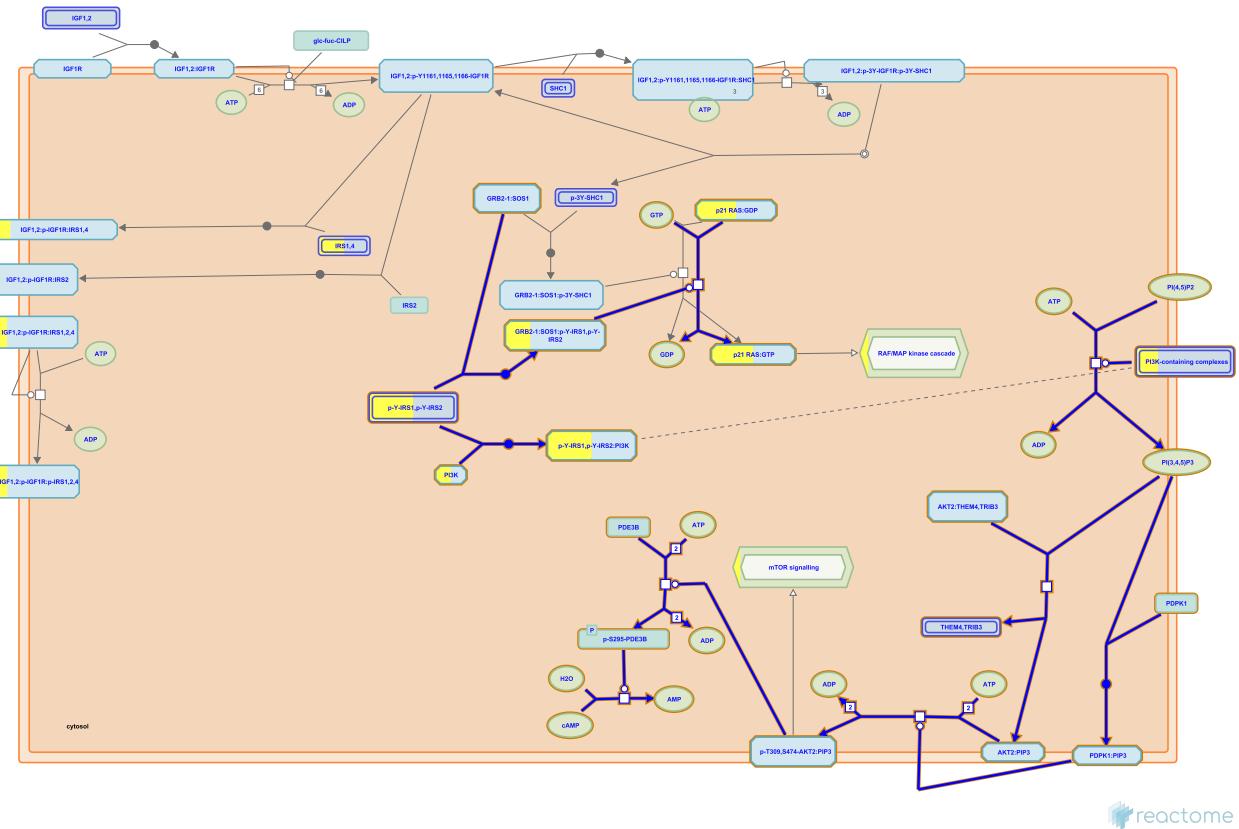
Insulin binding to its receptor results in receptor autophosphorylation on tyrosine residues and the tyrosine phosphorylation of insulin receptor substrates (e.g. IRS and Shc) by the insulin receptor tyrosine kinase. This allows association of IRSs with downstream effectors such as PI-3K via its Src homology 2 (SH2) domains leading to end point events such as Glut4 (Slc2a4) translocation. Shc when tyrosine phosphorylated associates with Grb2 and can thus activate the Ras/MAPK pathway independent of the IRSs.

Signal transduction by the insulin receptor is not limited to its activation at the cell surface. The activated ligand-receptor complex initially at the cell surface, is internalised into endosomes itself a process which is dependent on tyrosine autophosphorylation. Endocytosis of activated receptors has the dual effect of concentrating receptors within endosomes and allows the insulin receptor tyrosine kinase to phosphorylate substrates that are spatially distinct from those accessible at the plasma membrane. Acidification of the endosomal lumen, due to the presence of proton pumps, results in dissociation of insulin from its receptor. (The endosome constitutes the major site of insulin degradation). This loss of the ligand-receptor complex attenuates any further insulin-driven receptor re-phosphorylation events and leads to receptor dephosphorylation by extra-luminal endosomally-associated protein tyrosine phosphatases (PTPs). The identity of these PTPs is not clearly established yet. A discussion of candidates will be added in the near future.

References

- White M F, Kahn C R, The insulin signaling system., J Biol Chem, 269, 1994, 1-4, 8276779.

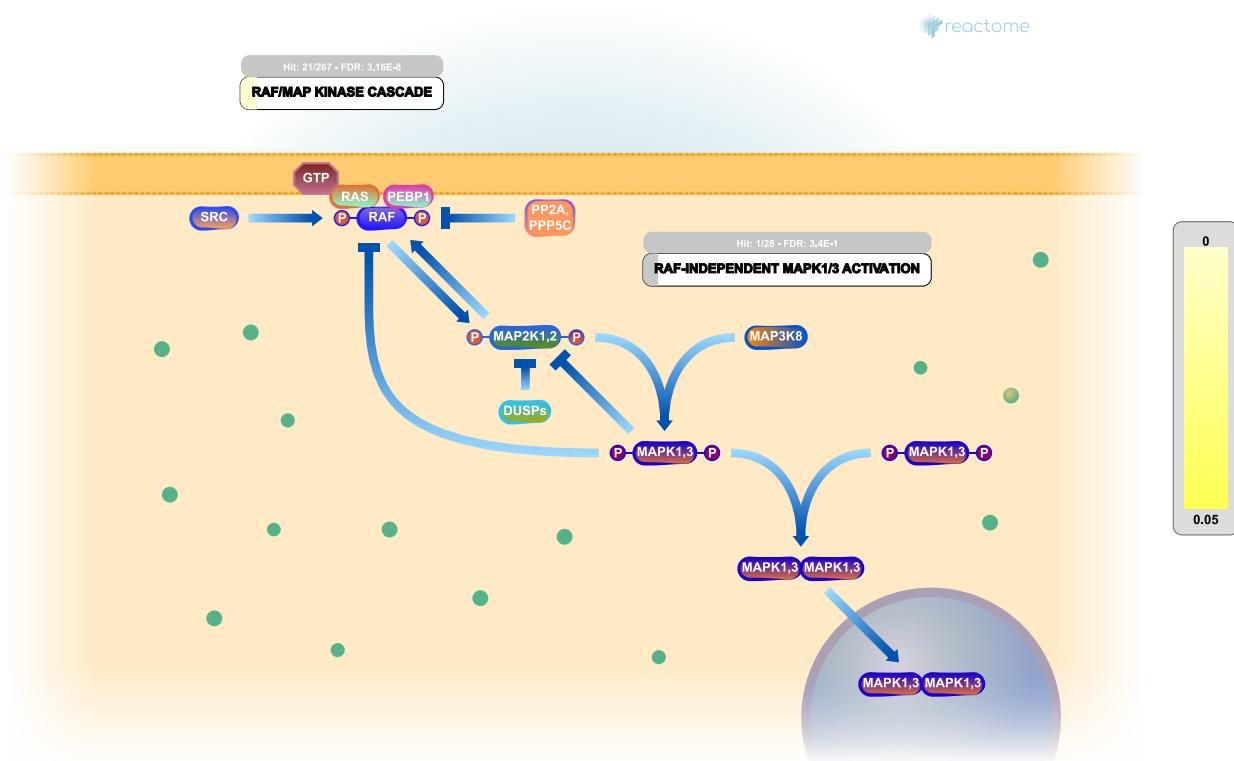
2.18 IRS-mediated signalling (R-HSA-112399)



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.

2.19 MAPK1/MAPK3 signaling (R-HSA-5684996)

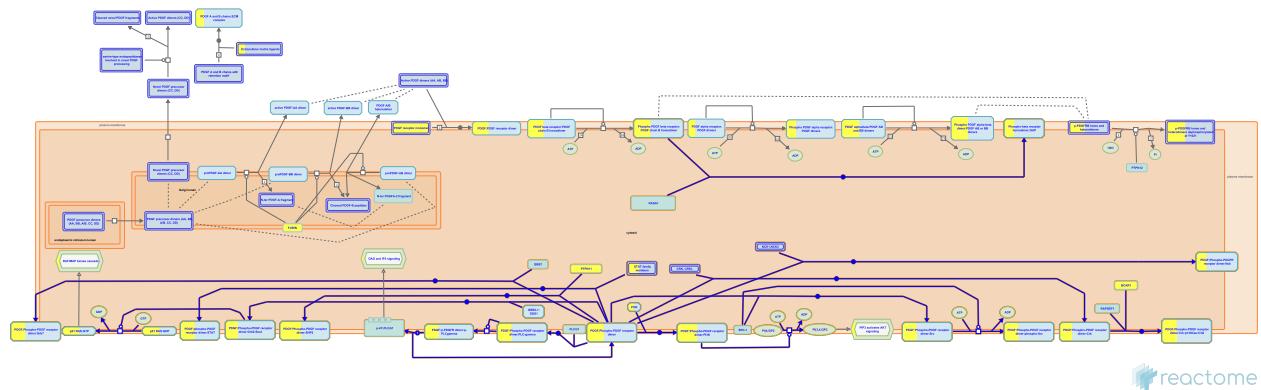


The extracellular signal regulated kinases (ERKs) 1 and 2, also known as MAPK3 and MAPK1, are phosphorylated by the MAP2Ks 1 and 2 in response to a wide range of extracellular stimuli to promote differentiation, proliferation, cell motility, cell survival, metabolism and transcription, among others (reviewed in Roskoski, 2012b; McKay and Morrison, 2007; Raman et al, 2007). In the classical pathway, MAPK1/3 activation is triggered by the GEF-mediated activation of RAS at the plasma membrane, leading to the activation of the RAF MAP3Ks (reviewed in McKay and Morrison, 2007; Matallanas et al, 2011; Wellbrock et al, 2004). However, many physiological and pathological stimuli have been found to activate MAPK1/3 independently of RAF and RAS, acting instead through MAP3Ks such as MOS, TPL2 and AMPK (Dawson et al, 2008; Wang et al, 2009; Kuriakose et al, 2014; Awane et al, 1999). Activated MAPK1/3 phosphorylate numerous targets in both the nucleus and cytoplasm (reviewed in Yoon and Seger, 2006; Roskoski 2012b).

References

- Roskoski Robert Jr, ERK1/2 MAP kinases: structure, function, and regulation, Pharmacol. Res., 66, 2012, 105-43, 22569528.
- McKay, Morrison Deborah K, Integrating signals from RTKs to ERK/MAPK, Oncogene, 26, 2007, 3113-21, 17496910.
- Raman M, Chen W, Cobb M H, Differential regulation and properties of MAPKs, Oncogene, 26, 2007, 3100-12, 17496909.
- Matallanas David, Birtwistle Marc, Romano David, Zebisch Armin, Rauch Jens et al., Raf family kinases: old dogs have learned new tricks, Genes Cancer, 2, 2011, 232-60, 21779496.
- Wellbrock Claudia, Karasarides Maria, Marais Richard, The RAF proteins take centre stage, Nat Rev Mol Cell Biol, 5, 2004, 875-85, 15520807.

2.20 Downstream signal transduction (R-HSA-186763)



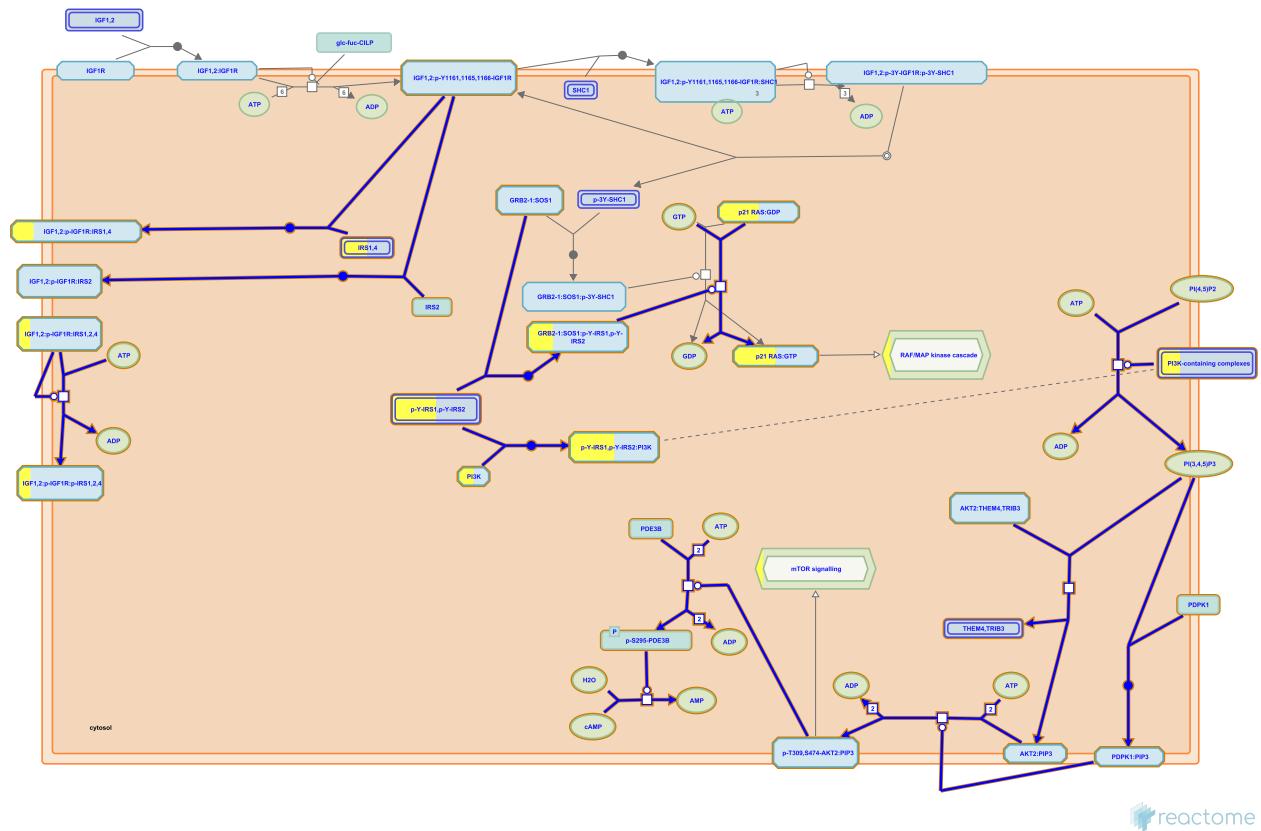
The role of autophosphorylation sites on PDGF receptors are to provide docking sites for downstream signal transduction molecules which contain SH2 domains. The SH2 domain is a conserved motif of around 100 amino acids that can bind a phosphorylated tyrosine residue. These downstream molecules are activated upon binding to, or phosphorylated by, the receptor kinases intrinsic to PDGF receptors.

Some of the downstream molecules are themselves enzymes, such as phosphatidylinositol 3'-kinase (PI3K), phospholipase C (PLC-gamma), the Src family of tyrosine kinases, the tyrosine phosphatase SHP2, and a GTPase activating protein (GAP) for Ras. Others such as Grb2 are adaptor molecules which link the receptor with downstream catalytic molecules.

References

- Heldin Carl-Henrik, Westermark, Mechanism of action and in vivo role of platelet-derived growth factor, *Physiol Rev*, 79, 1999, 1283-316, 10508235.
- Heldin Carl-Henrik, Ostman, Rnnstrand, Signal transduction via platelet-derived growth factor receptors, *Biochim Biophys Acta*, 1378, 1998, F79-113, 9739761.

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



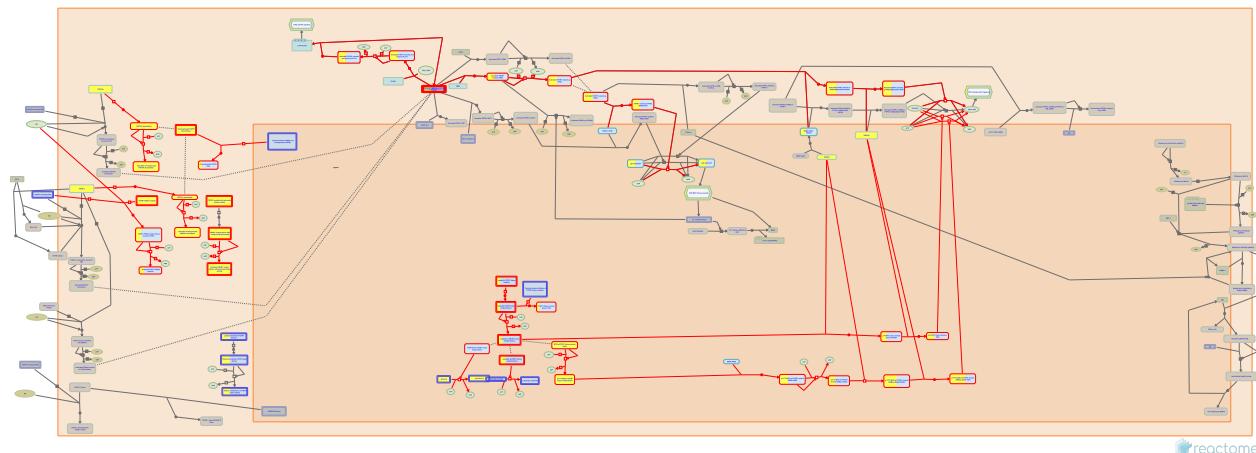
Cellular compartments: cytosol, plasma membrane.

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 Jasminka, Matijevi Tanja, Knezevi Jelena, Biological & physiological aspects of action of insulin-like growth factor peptide family, Indian J. Med. Res., 125, 2007, 511-22, 17598937.
- Parrella Edoardo, Longo Valter D, Insulin/IGF-I and related signaling pathways regulate aging in non-dividing cells: from yeast to the mammalian brain, ScientificWorldJournal, 10, 2010, 161-77, 20098959.
- Siddle Kenneth, Molecular basis of signaling specificity of insulin and IGF receptors: neglected corners and recent advances, Front Endocrinol (Lausanne), 3, 2012, 34, 22649417.
- Maki Robert G, Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer, J. Clin. Oncol., 28, 2010, 4985-95, 20975071.
- Annunziata Marta, Granata Riccarda, Ghigo Ezio, The IGF system, Acta Diabetol, 48, 2011, 1-9, 21042815.

2.22 Signaling by FGFR1 in disease (R-HSA-5655302)



Diseases: cancer, bone development disease.

The FGFR1 gene has been shown to be subject to activating mutations, chromosomal rearrangements and gene amplification leading to a variety of proliferative and developmental disorders depending on whether these events occur in the germline or arise somatically (reviewed in Webster and Donoghue, 1997; Burke, 1998; Cunningham, 2007; Wesche, 2011; Greulich and Pollock, 2011).

Activating mutation P252R in FGFR1 is associated with the development of Pfeiffer syndrome, characterized by craniosynostosis (premature fusion of several sutures in the skull) and broadened thumbs and toes (Muenke, 1994; reviewed in Cunningham, 2007). This residue falls in a highly conserved Pro-Ser dipeptide between the second and third Ig domains of the extracellular region of the receptor. The mutation is thought to increase the number of hydrogen bonds formed with the ligand and to thereby increase ligand-binding affinity (Ibrahim, 2004a). Unlike other FGF receptors, few activating point mutations in the FGFR1 coding sequence have been identified in cancer. Point mutations in the Ig II-III linker analogous to the P252R Pfeiffer syndrome mutation have been identified in lung cancer and melanoma (Ruhe, 2007; Davies, 2005), and two kinase-domain mutations in FGFR1 have been identified in glioblastoma (Rand, 2005, Network TCGA, 2008).

In contrast, FGFR1 is a target of chromosomal rearrangements in a number of cancers. FGFR1 has been shown to be recurrently translocated in the 8p11 myeloproliferative syndrome (EMS), a pre-leukemic condition also known as stem cell leukemia/lymphoma (SCLL) that rapidly progresses to leukemia. This translocation fuses the kinase domain of FGFR1 with the dimerization domain of one of 10 identified fusion partners, resulting in the constitutive dimerization and activation of the kinase (reviewed in Jackson, 2010).

Amplification of the FGFR1 gene has been implicated as a oncogenic factor in a range of cancers, including breast, ovarian, bladder, lung, oral squamous carcinomas, and rhabdomyosarcoma (reviewed in Turner and Grose, 2010; Wesche, 2011; Greulich and Pollock, 2011), although there are other candidate genes in the amplified region and the definitive role of FGFR1 has not been fully established.

More recently, FGFR1 fusion proteins have been identified in a number of cancers; these are thought to undergo constitutive ligand-independent dimerization and activation based on dimerization motifs found in the fusion partners (reviewed in Parker, 2014).

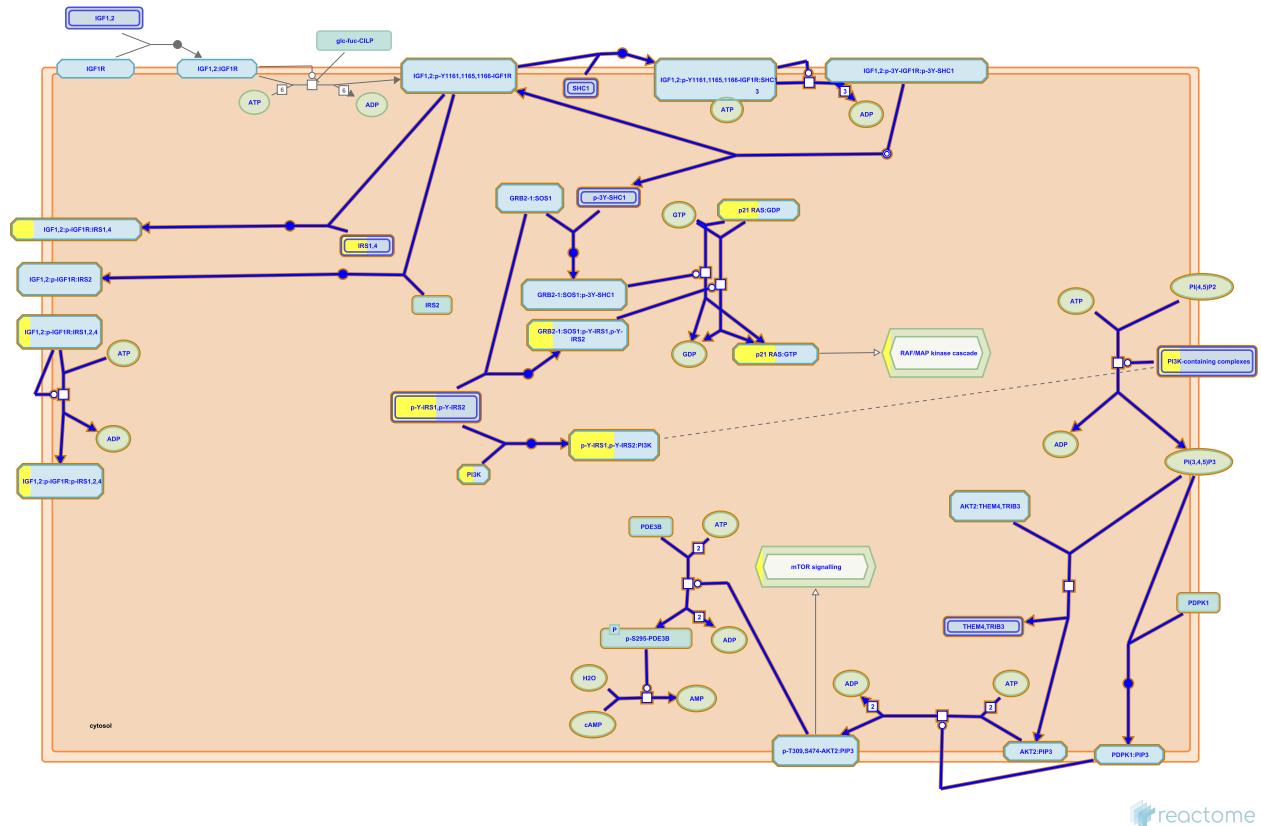
References

- Webster Melanie K, Donoghue Daniel J, FGFR activation in skeletal disorders: too much of a good thing, *Trends Genet*, 13, 1997, 178-82, 9154000.
- Burke David, Wilkes David, Blundell Tom L, Malcolm Sue, Fibroblast growth factor receptors: lessons from the genes, *Trends Biochem Sci*, 23, 1998, 59-62, 9538690.
- Cunningham Michael L, Seto Marianne L, Ratisoontorn Chootima, Heike Carrie L, Hing Anne V, Syndromic craniosynostosis: from history to hydrogen bonds, *Orthod Craniofac Res*, 10, 2007, 67-81,

17552943.

- Wesche Jorgen, Haglund Kaisa, Haugsten Ellen Margrethe, Fibroblast growth factors and their receptors in cancer, *Biochem J*, 437, 2011, 199-213, 21711248.
- Greulich Heidi, Pollock Pamela M, Targeting mutant fibroblast growth factor receptors in cancer, *Trends Mol Med*, 17, 2011, 283-92, 21367659.

2.23 IGF1R signaling cascade (R-HSA-2428924)



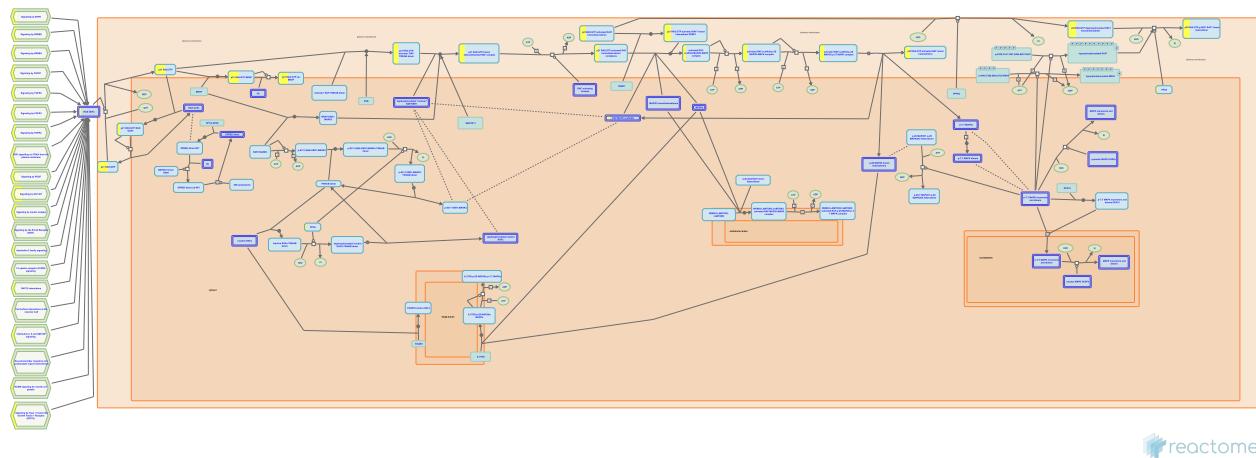
Cellular compartments: cytosol, plasma membrane.

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 Jasminka, Matijevi Tanja, Knezevi Jelena, Biological & physiological aspects of action of insulin-like growth factor peptide family, Indian J. Med. Res., 125, 2007, 511-22, 17598937.
- Parrella Edoardo, Longo Valter D, Insulin/IGF-I and related signaling pathways regulate aging in non-dividing cells: from yeast to the mammalian brain, ScientificWorldJournal, 10, 2010, 161-77, 20098959.
- Siddle Kenneth, Molecular basis of signaling specificity of insulin and IGF receptors: neglected corners and recent advances, Front Endocrinol (Lausanne), 3, 2012, 34, 22649417.
- Maki Robert G, Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer, J. Clin. Oncol., 28, 2010, 4985-95, 20975071.
- Annunziata Marta, Granata Riccarda, Ghigo Ezio, The IGF system, Acta Diabetol, 48, 2011, 1-9, 21042815.

2.24 RAF/MAP kinase cascade (R-HSA-5673001)



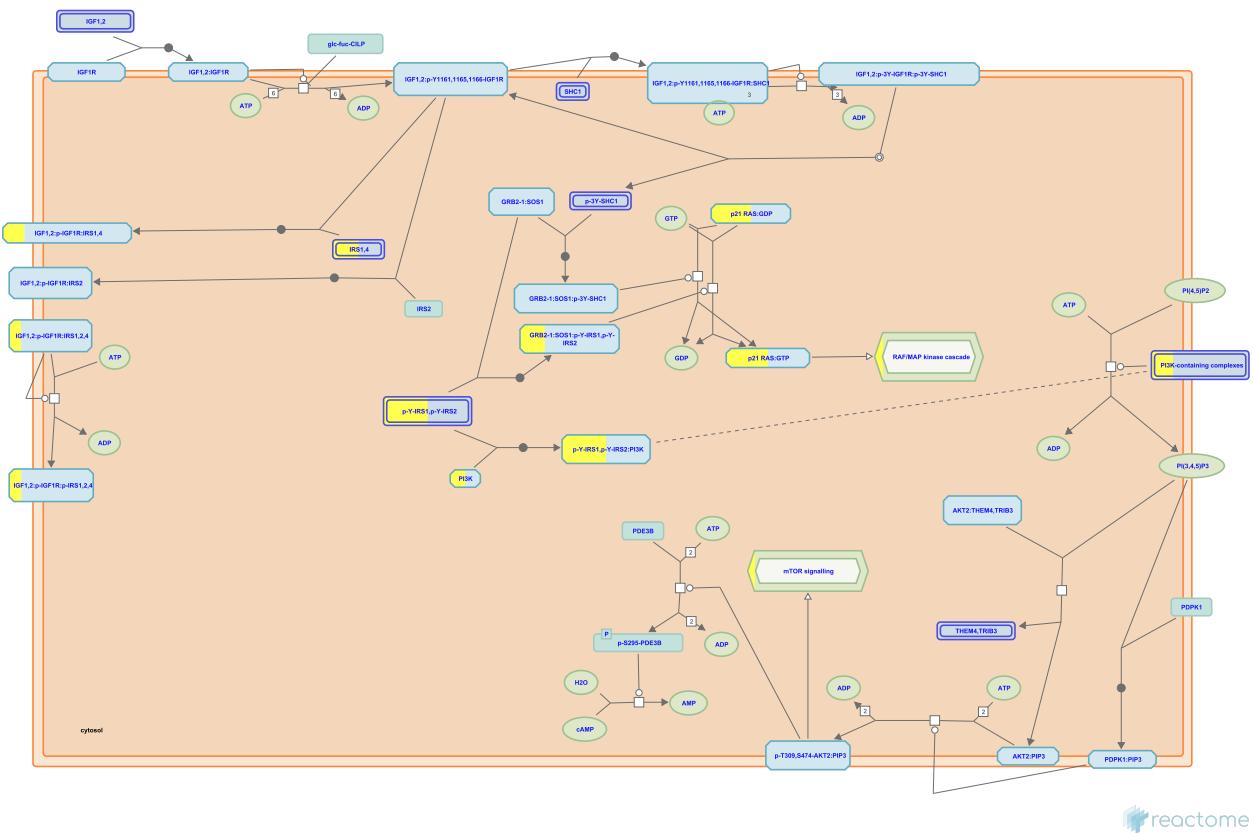
The RAS-RAF-MEK-ERK pathway regulates processes such as proliferation, differentiation, survival, senescence and cell motility in response to growth factors, hormones and cytokines, among others. Binding of these stimuli to receptors in the plasma membrane promotes the GEF-mediated activation of RAS at the plasma membrane and initiates the three-tiered kinase cascade of the conventional MAPK cascades. GTP-bound RAS recruits RAF (the MAPK kinase kinase), and promotes its dimerization and activation (reviewed in Cseh et al, 2014; Roskoski, 2010; McKay and Morrison, 2007; Wellbrock et al, 2004). Activated RAF phosphorylates the MAPK kinase proteins MEK1 and MEK2 (also known as MAP2K1 and MAP2K2), which in turn phosphorylate the proline-directed kinases ERK1 and 2 (also known as MAPK3 and MAPK1) (reviewed in Roskoski, 2012a, b; Kryiakis and Avruch, 2012). Activated ERK proteins may undergo dimerization and have identified targets in both the nucleus and the cytosol; consistent with this, a proportion of activated ERK protein relocates to the nucleus in response to stimuli (reviewed in Roskoski 2012b; Turjanski et al, 2007; Plotnikov et al, 2010; Cagnello et al, 2011). Although initially seen as a linear cascade originating at the plasma membrane and culminating in the nucleus, the RAS/RAF MAPK cascade is now also known to be activated from various intracellular location. Temporal and spatial specificity of the cascade is achieved in part through the interaction of pathway components with numerous scaffolding proteins (reviewed in McKay and Morrison, 2007; Brown and Sacks, 2009).

The importance of the RAS/RAF MAPK cascade is highlighted by the fact that components of this pathway are mutated with high frequency in a large number of human cancers. Activating mutations in RAS are found in approximately one third of human cancers, while ~8% of tumors express an activated form of BRAF (Roberts and Der, 2007; Davies et al, 2002; Cantwell-Dorris et al, 2011).

References

- Cseh Botond, Doma Eszter, Baccarini Manuela, "RAF" neighborhood: protein-protein interaction in the Raf/Mek/Erk pathway, FEBS Lett., 588, 2014, 2398-406, 24937142.
- Roskoski Robert Jr, RAF protein-serine/threonine kinases: structure and regulation, Biochem. Biophys. Res. Commun., 399, 2010, 313-7, 20674547.
- McKay, Morrison Deborah K, Integrating signals from RTKs to ERK/MAPK, Oncogene, 26, 2007, 3113-21, 17496910.
- Wellbrock Claudia, Karasarides Maria, Marais Richard, The RAF proteins take centre stage, Nat Rev Mol Cell Biol, 5, 2004, 875-85, 15520807.
- Roskoski Robert Jr, ERK1/2 MAP kinases: structure, function, and regulation, Pharmacol. Res., 66, 2012, 105-43, 22569528.

2.25 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 Kenneth, Molecular basis of signaling specificity of insulin and IGF receptors: neglected corners and recent advances, *Front Endocrinol (Lausanne)*, 3, 2012, 34, 22649417.
- Annunziata Marta, Granata Riccarda, Ghigo Ezio, The IGF system, *Acta Diabetol*, 48, 2011, 1-9, 21042815.
- Maki Robert G, Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer, *J. Clin. Oncol.*, 28, 2010, 4985-95, 20975071.
- Chitnis Meenali M, Yuen John S P, Protheroe Andrew S, Pollak Michael, Macaulay Valentine M, The type 1 insulin-like growth factor receptor pathway, *Clin. Cancer Res.*, 14, 2008, 6364-70, 18927274.
- Parrella Edoardo, Longo Valter D, Insulin/IGF-I and related signaling pathways regulate aging in non-dividing cells: from yeast to the mammalian brain, *ScientificWorldJournal*, 10, 2010, 161-77, 20098959.