Report for Analysis tools Review

Administrative

This report is intend for reviewer of the pathway analysis:MjAxNzEyMTgwNjM0MDJfMjI%3D (please note that this URL maybe out of date because of the token can expired at our server end) and your input identifiers are :O95831, Q8IWV1, Q13214, P35716, O43692.... It has been automatically generated in Reactome version 63 at 16:42 10-01-2018.

Introduction

Each reaction (pathway event) is represented here by a simple diagram. Input molecules are shown as labelled boxes (left side) connected by plain lines to a central square. Arrowed lines connect the central square to the output molecules (right side). If relevant, catalyst molecules are represented above the central square, connected to it by a red arrowed line. Input molecules that are also the catalyst (e.g. signaling or enzyme/substrate complexes) are shown on the left and joined to the central node by a red arrowed line. The names of reactions that precede/follow in the pathway are shown as text on the far left/far right respectively.

Summary text may appear to be overlapping or redundant. Please remember that this document is extracted from multiple pages on the Reactome website, this redundancy is useful to provide context for users who might first arrive at a mid-point in the pathway. Suggestions for improvement are welcome.

Reactome represents human biology. Literature references that demonstrate the occurrence of the reaction in humans are given preference, they are not intended to provide a historical record. Unfortunately we do not have the resources to identify all relevant references, but we are happy to cite any that you feel should be included.In your review, we would appreciate it if you could verify that the events that we describe (pathways and reactions) are annotated clearly and that the molecular details of the reactions are accurate.

In your review, we would appreciate it if you could verify that the events that we describe (pathways and reactions) are annotated clearly and that the molecular details of the reactions are accurate.

A more detailed representation of the pathway as a diagram can be found on our website. We would appreciate your feedback on the content and navigability of the website. A short tutorial of the Pathway Browser can be found at the top of the webpage. The zoomable pathway diagram is interactive. Text descriptions are revealed in the panel below the diagram under the Overview tab. To view a text description, select a participating molecule or reaction node in the diagram. Clicking on an event in the hierarchy in the left panel will highlight the event(s) in the diagram and a text description will be displayed in the panel below

Take a look at our's literature for more information:

The Reactome pathway Knowledgebase,Nucleic Acids Research, Volume 44, Issue D1, 4 January 2016, Pages D481–D487

Open Targets: a platform for therapeutic target identification and validation,Nucleic Acids Research, Volume 45, Issue D1, 4 January 2017, Pages D985–D994

Reactome enhanced pathway visualization,Bioinformatics, Volume 33, Issue 21, 1 November 2017, Pages 3461–3467

Summary

1. 164 of 184 identifiers you submitted was Found in Reactome.

2. 924 pathways was hit in Reactome total {} pathways.

3. 20 of top Enhanced/Overrepresented pathways was list based on p-Value.

4. The "fireworks" diagram for this pathway analysis:

Overview

1. Top 20 Overrepresentation pathways sorted by p-Value.

Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total	Reactions ratio	Species name
Diseases of signal transduction	50	467	0.0345	1.11022e-16	2.84217e-14	225	297	0.0265	Homo sapiens
Signaling by Receptor Tyrosine Kinases	53	585	0.0432	1.11022e-16	2.84217e-14	375	625	0.0557	Homo sapiens
Signal Transduction	102	3024	0.2231	1.11022e-16	2.84217e-14	816	1958	0.1745	Homo sapiens
PI3K/AKT Signaling in Cancer	25	126	0.0093	1.11022e-16	2.84217e-14	8	21	0.0019	Homo sapiens
Intracellular signaling by second messengers	32	347	0.0256	2.22045e-16	4.55191e-14	33	104	0.0093	Homo sapiens
PIP3 activates AKT signaling	30	309	0.0228	5.55112e-16	9.43690e-14	30	85	0.0076	Homo sapiens
Negative regulation of the PI3K/AKT network	21	126	0.0093	6.66134e-16	9.72555e-14	4	10	0.0009	Homo sapiens
PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling	19	118	0.0087	3.13083e-14	3.57847e-12	2	7	0.0006	Homo sapiens
Signaling by FGFR in disease	17	87	0.0064	3.48610e-14	3.57847e-12	74	106	0.0094	Homo sapiens
Disease	62	1503	0.1109	3.50830e-14	3.57847e-12	275	905	0.0807	Homo sapiens
Signaling by SCF-KIT	14	50	0.0037	5.75096e-14	5.34839e-12	33	36	0.0032	Homo sapiens
Constitutive Signaling by Aberrant PI3K in Cancer	17	95	0.0070	1.40443e-13	1.19377e-11	2	2	0.0002	Homo sapiens
Signaling by VEGF	19	134	0.0099	2.85660e-13	2.22815e-11	42	83	0.0074	Homo sapiens
VEGFA-VEGFR2 Pathway	17	125	0.0092	1.01419e-11	7.40358e-10	39	77	0.0069	Homo sapiens
Insulin receptor signalling cascade	13	68	0.0050	5.01769e-11	3.41203e-09	15	25	0.0022	Homo sapiens
Signaling by PDGF	13	69	0.0051	5.98870e-11	3.83277e-09	25	28	0.0025	Homo sapiens
Signaling by Insulin receptor	14	93	0.0069	1.96191e-10	1.05170e-08	23	34	0.0030	Homo sapiens
IRS-mediated signalling	12	61	0.0045	2.04588e-10	1.05170e-08	4	9	0.0008	Homo sapiens
MAPK1/MAPK3 signaling	22	274	0.0202	2.06215e-10	1.05170e-08	19	46	0.0041	Homo sapiens
Downstream signal transduction	10	36	0.0027	2.60381e-10	1.24983e-08	16	16	0.0014	Homo sapiens

2. Pathway details.

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

Summation

species name:Homo sapiens,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.

List of identifiers was found at this pathway

P01111	P04626	P01116	P37173	P27986	P21860
Q00987	P42345	P42224	P46940	P21802	P40763
P60484	P49815	P35568	Q06124	P55211	P16234
P11274	P07900	P00533	O15164	P02751	P42336
P46531	P22681	Q15465	P10721	P09619	Q09472
P11362	Q13485	Q7Z5R6	Q14738	P35222	O43524
P98177	P05106	Q969H0	P08581	P78504	

Authors

D'Eustachio, Peter, 2015-01-15

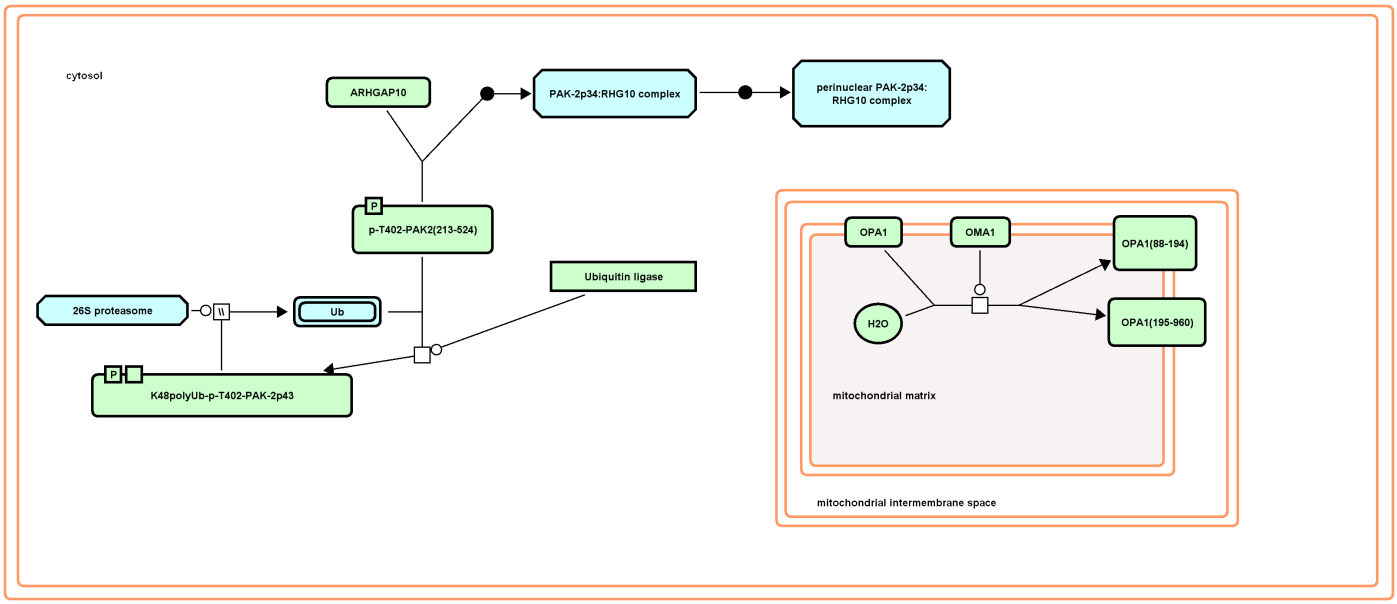
Editors

Shorser, Solomon, 2016-11-07

References

"The evolution of signalling pathways in animal development",Nat. Rev. Genet.,4,2003,39-49.

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



Summation

species name:Homo sapiens,Receptor tyrosine kinases (RTKs) are a major class of cell surface proteins involved in Signal Transduction. Human cells contain ~60 RTKs, grouped into 20 subfamilies based on their domain architecture. All RTK subfamilies are

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

List of identifiers was found at this pathway

P09958	P01111	P56945	O43184	P04626	P01116
P27986	P21860	P42345	P42224	P21802	P40763
Q05513	P51812	P35568	Q06124	P17252	P16234
P07900	P02452	P35916	O14757	P07948	O15264
P00533	P17948	P02751	P29474	P42336	P22681
P06213	P05771	Q13164	P10721	P09619	P11362
P08123	P02461	Q05655	Q14738	P35222	P05106
P08581	O15524	Q14185	P52735	P36543	P12110

Authors

Rothfels, Karen, 2017-05-23

Editors

Schmidt, Esther

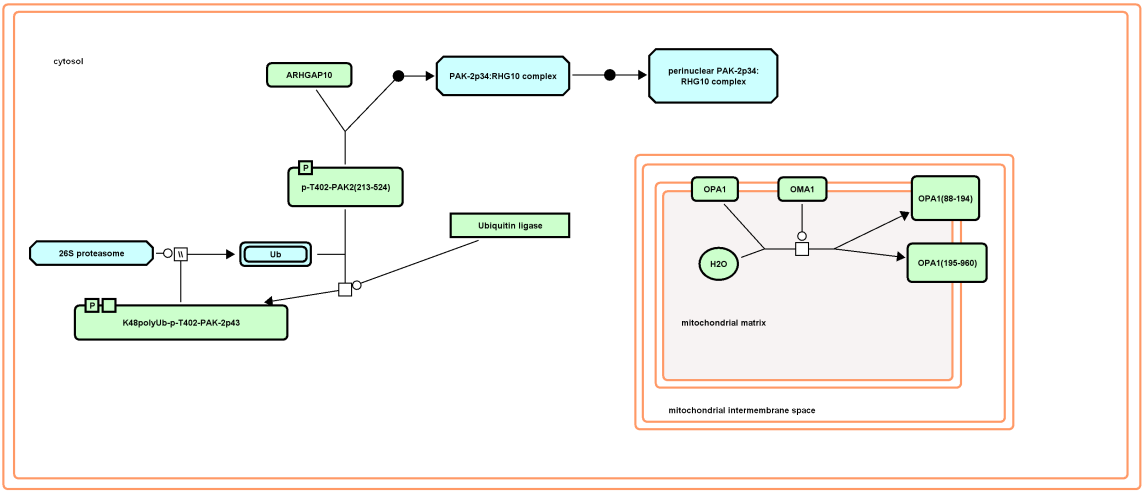
Reviewers

D'Eustachio, Peter, 2017-06-22

References

"The RAF proteins take centre stage",Nat Rev Mol Cell Biol,5,2004,875-85.

2.3. Signal Transduction (R-HSA-162582)



Summation

species name:Homo sapiens,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).

List of identifiers was found at this pathway

P09958	P56945	P49454	Q13145	O43184	P37173
P49674	P28336	Q00987	O14686	P63092	P40763
P60484	O14746	Q05513	P49619	P51812	P35568
P55211	P16234	Q9UPN9	P07948	O15264	P02751
P06213	P11362	Q86UP2	P21802	P01116	P08151
Q13164	P04083	P01111	Q15465	P27986	P02461

O60346	P17948	P63096	P07900	P04637	Q7Z5R6
Q09472	Q15119	P01023	P98177	P05106	Q05655
P17252	Q96GD4	P46531	P09544	Q92574	P29474
P42336	O14757	P08581	P04626	P35222	P11274
P78504	Q9NQC7	P21860	P42345	P42224	Q9Y4A5
P46940	P49815	Q06124	P02452	P35916	Q13635
P00533	P22681	P05771	P10071	P10721	P09619
P08123	Q13485	Q01974	P29590	Q14738	O43524
Q969H0	Q9Y561	Q16760	O15524	Q14185	Q9NRY4
P52735	P36543	P12110			

Authors

Joshi-Tope, G, 2005-03-31 19:40:53

Editors

Schmidt, Esther

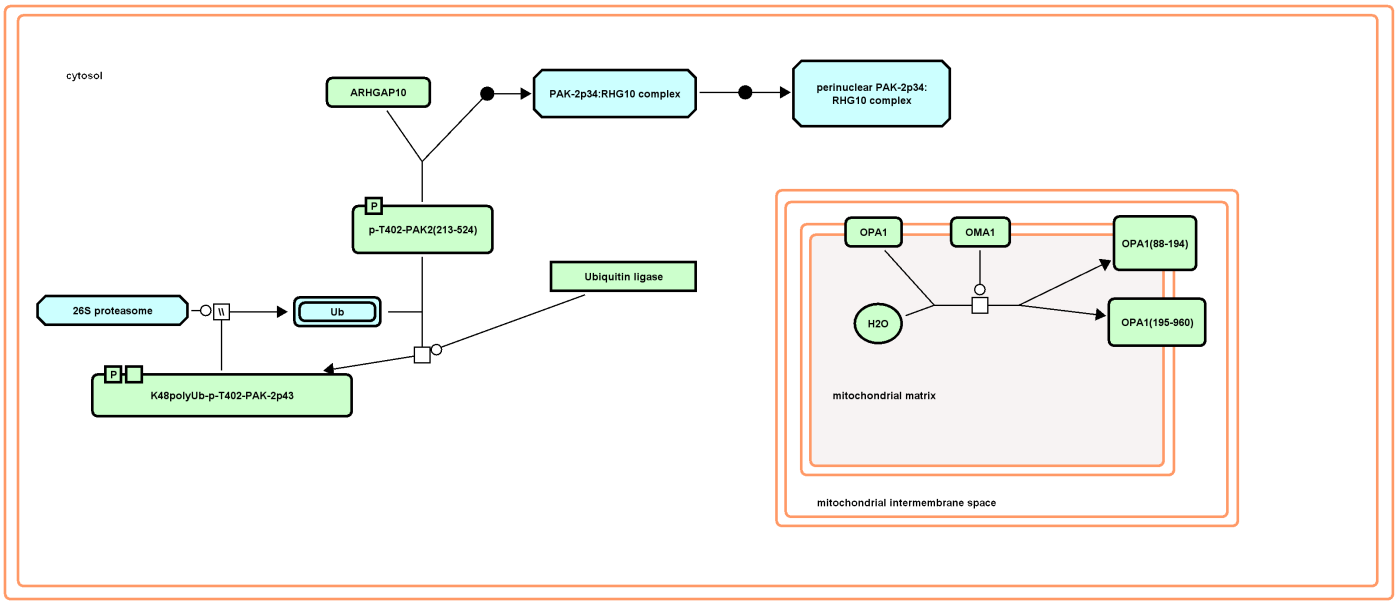
Reviewers

Barroso, I, Stanley, FM, Joutel, A, Rush, MG, 0000-00-00 00:00:00

References

"Feedback regulation of EGFR signalling: decision making by early and delayed loops",Nat Rev Mol Cell Biol,12,2011,104-17.

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



Summation

species name:Homo sapiens,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.

List of identifiers was found at this pathway

P09619	P04626	P21802	P10721	P21860	P27986
P42345	Q00987	P60484	P49815	P35568	Q06124
P55211	P16234	P11362	O43524	P98177	P00533

P08581 P42336

Authors

Orlic-Milacic, M, 2012-05-01

Editors

Orlic-Milacic, Marija, 2015-02-12

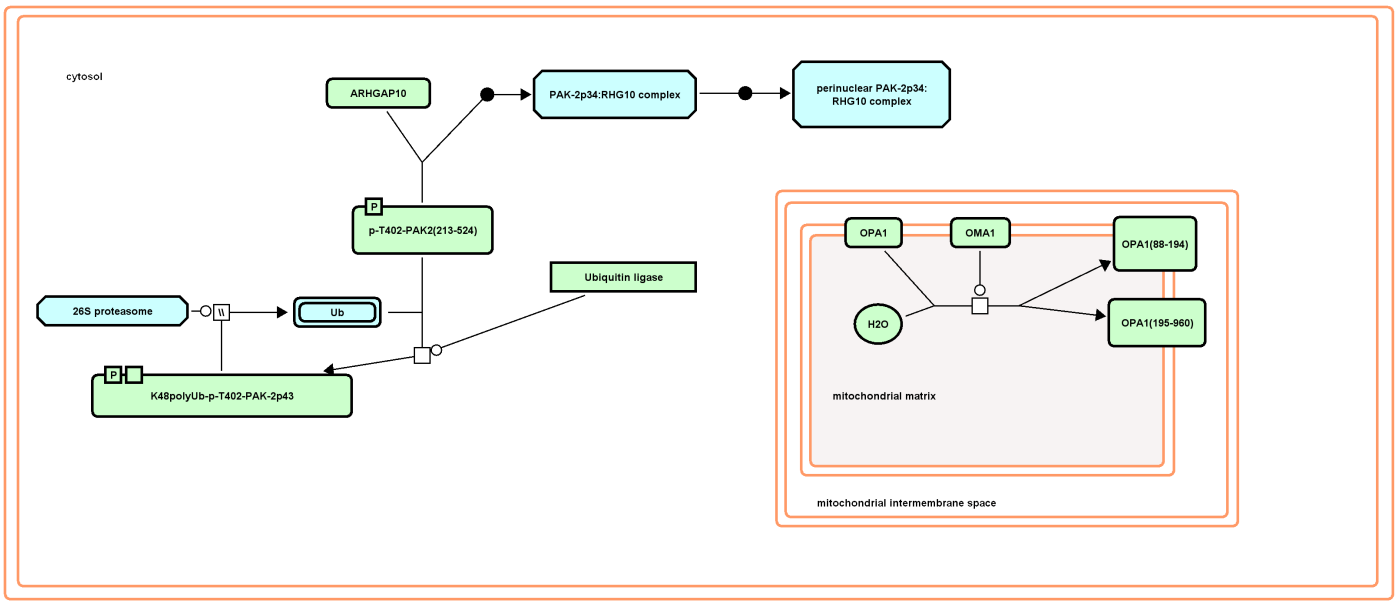
Reviewers

Thorpe, Lauren, 2012-08-13

References

"PTEN loss in the continuum of common cancers, rare syndromes and mouse models",Nat. Rev. Cancer,11,2011,289-301.

2.5. Intracellular signaling by second messengers (R-HSA-9006925)



Summation

species name:Homo sapiens,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).

List of identifiers was found at this pathway

P09619	P04626	P21802	P10721	P21860	P27986
P42345	Q00987	P06213	O60346	P60484	P49815
P29590	Q05655	P35568	Q06124	P04637	P55211
P17252	Q14738	P16234	P11362	O43524	P98177
P00533	P08581	P42336			

Authors

Rothfels, Karen, 2017-05-23

Editors

Schmidt, Esther

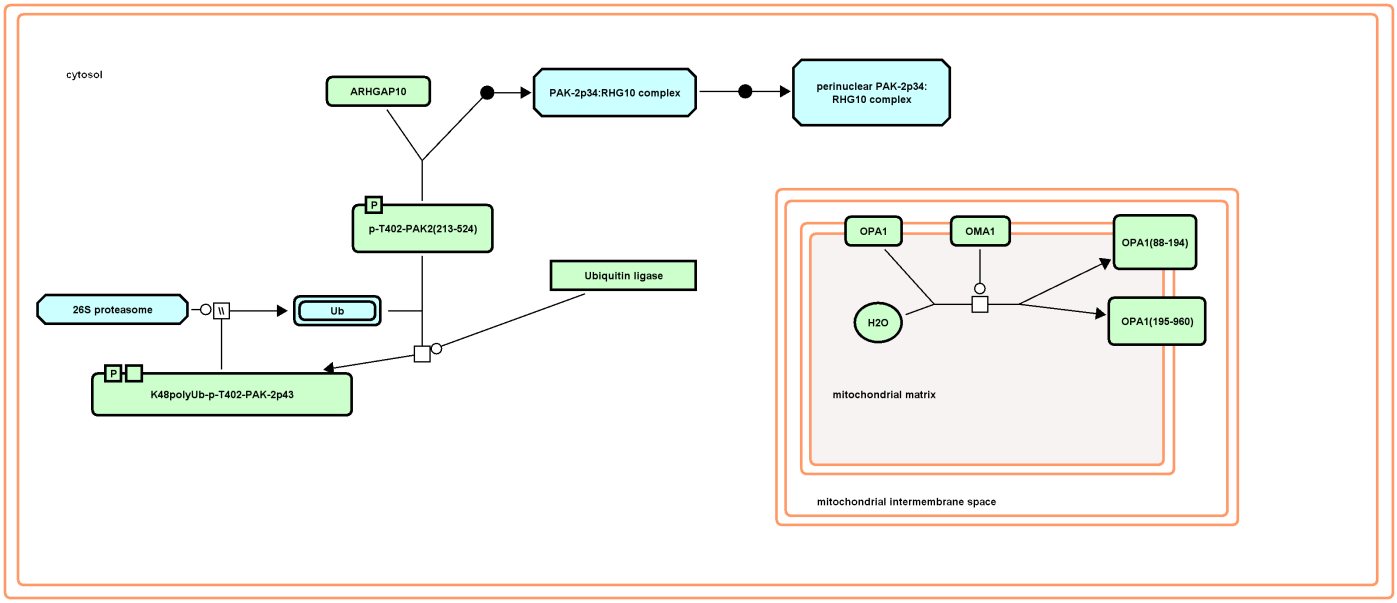
Reviewers

D'Eustachio, Peter, 2017-06-22

References

"Calcium signaling and cell proliferation",Cell. Signal.,27,2015,2139-49.

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



Summation

species name:Homo sapiens,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 ustimulated 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 PDPK1 (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.

List of identifiers was found at this pathway

P09619	P04626	P21802	P10721	P21860	P27986
P42345	Q00987	P06213	O60346	P60484	P49815
P29590	P35568	Q06124	P04637	P55211	Q14738
P16234	P11362	O43524	P98177	P00533	P08581
P42336					

Authors

Orlic-Milacic, Marija, 2011-05-02

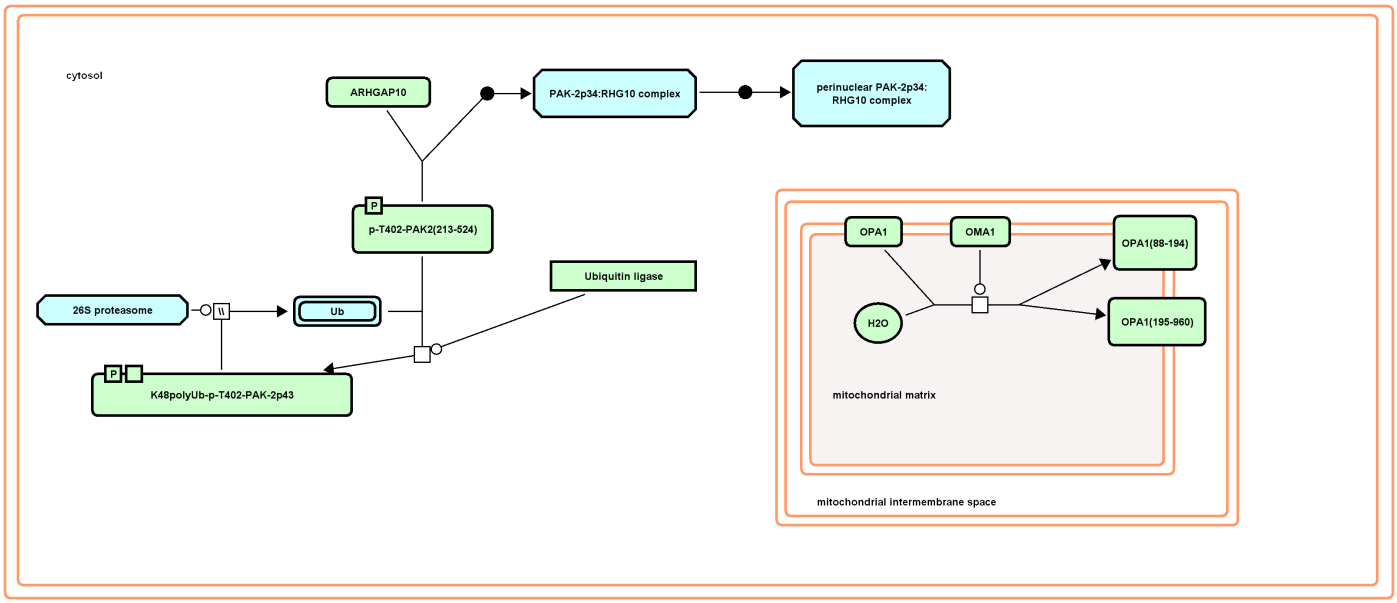
Editors

Schmidt, Esther

Reviewers

Greene, LA, 2007-11-08 15:39:37

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



Summation

species name:Homo sapiens,The PI3K/AKT network is negatively regulated by phosphatases that dephosphorylate PIP3, thus hampering AKT activation.

List of identifiers was found at this pathway

P09619	P04626	P21802	P10721	P21860	P27986
P06213	O60346	P60484	P35568	Q06124	Q14738
P16234	P11362	P00533	P08581	P42336	

Authors

Jassal, B, 2007-07-10 12:01:00

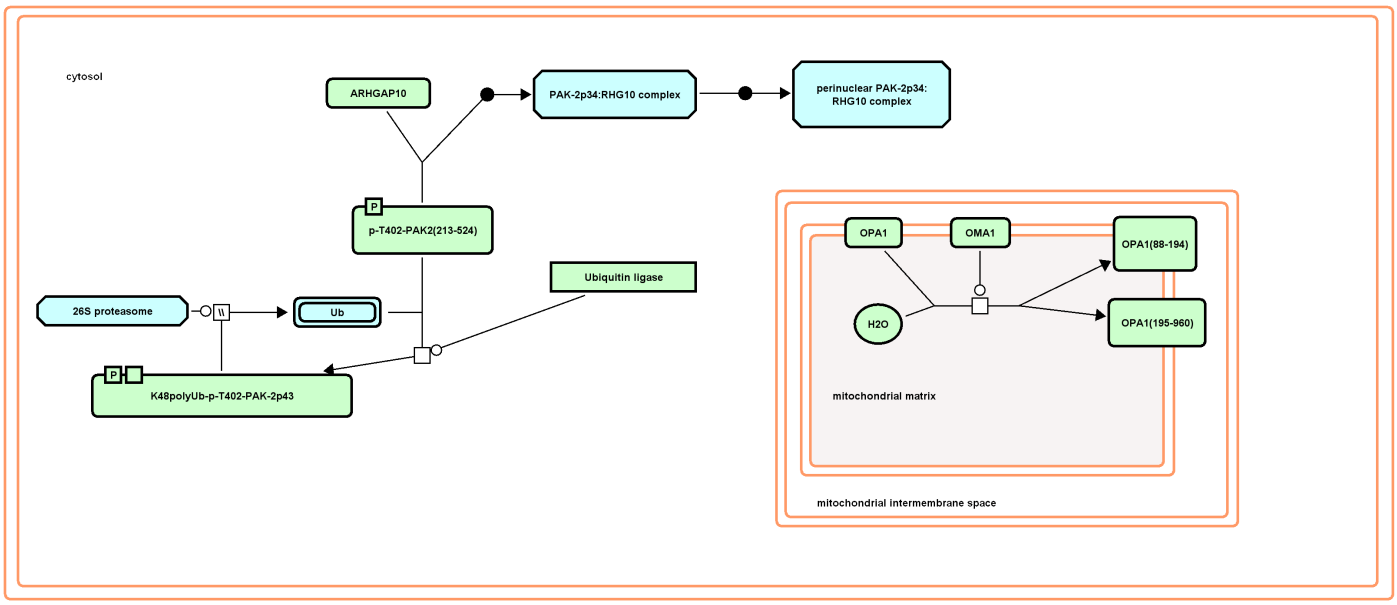
Editors

Croft, D

Reviewers

Greene, LA, 2007-11-08 15:39:37

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



Summation

species name:Homo sapiens,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.

List of identifiers was found at this pathway

P09619	P04626	P21802	P10721	P21860	P27986
P06213	P35568	Q06124	Q14738	P16234	P11362
P00533	P08581	P42336			

Authors

Orlic-Milacic, Marija, 2015-11-19

Editors

Croft, D

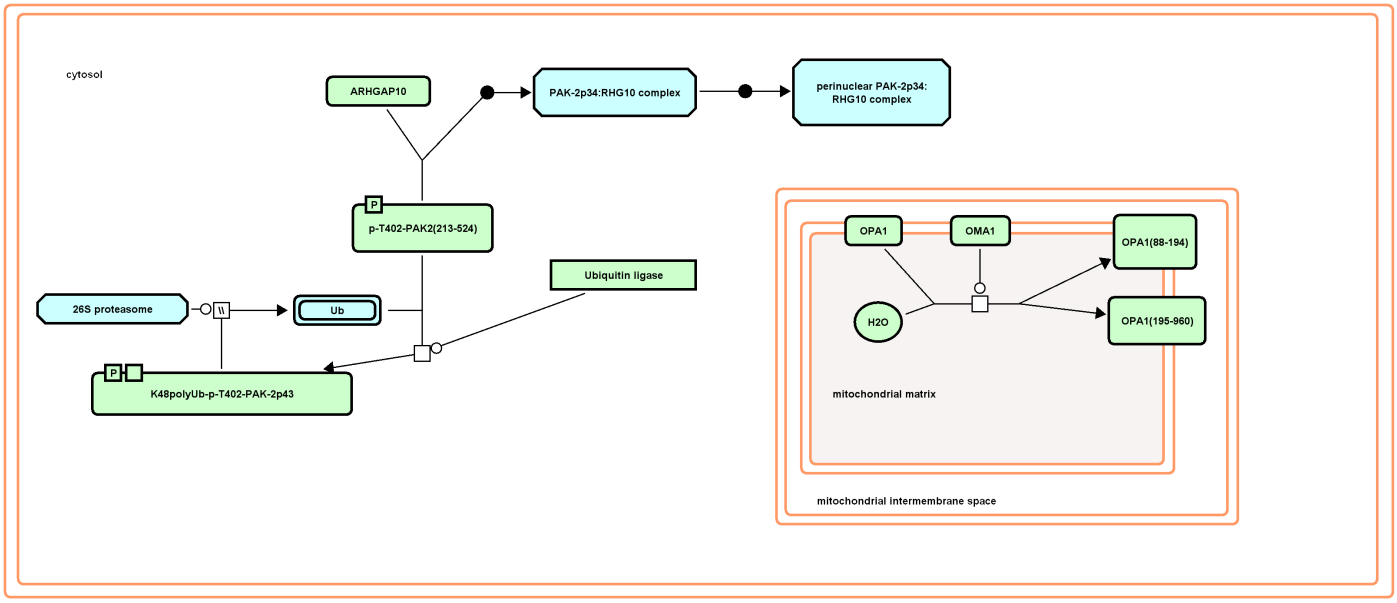
Reviewers

Porteu, Françoise, 2016-02-08

References

"PtdIns5P protects Akt from dephosphorylation through PP2A inhibition",Biochem. Biophys. Res. Commun.,387,2009,127-31.

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



Summation

species name:Homo sapiens,A number of skeletal and developmental diseases have been shown to arise as a result of mutations in the FGFR1, 2 and 3 genes. These include dwarfism syndromes (achondroplasia, hypochondroplasia and the neonatal lethal disorders thanatophoric dysplasia I and II), as well as craniosynostosis disorders such as Pfeiffer, Apert, Crouzon, Jackson-Weiss and Muenke syndromes (reviewed in Webster and Donoghue 1997; Burke, 1998, Cunningham, 2007; Harada, 2009). These mutations fall into four general regions of the receptor: a) the immunoglobulin (Ig)-like domain II-III linker region, b) the alternatively spliced second half of the Ig III domain, c) the transmembrane domain and d) the tyrosine kinase domain (reviewed in Webster and Donoghue, 1997). With the exception of mutations in class b), which affect only the relevant splice variant, these mutations may be present in either the 'b' or 'c' isoforms. These activating mutations affect FGFR function by altering or expanding the ligand-binding range of the receptors (see for instance Ibrahimi, 2004a), by promoting ligand-independent dimerization (for instance, Galvin,1996; Neilson and Friesel, 1996; d'Avis,1998) or by increasing the activity of the kinase domain (for instance, Webster, 1996; Naski, 1996; Tavormina, 1999; Bellus, 2000). Thus, a number of the point mutations found in FGFR receptors alter their activity without altering their intrinsic kinase activity. Many of the mutations that promote constitutive dimerization do so by creating or removing cysteine residues; the presence of an unpaired cysteine in the receptor is believed to promote dimerization through the formation of intramolecular disulphide bonds (Galvin, 1996; Robertson, 1998). Paralogous

mutations at equivalent positions have been identified in more than one FGF receptor, sometimes giving rise to different diseases. For instance, mutation of the highly conserved FGFR2 Ser252-Pro253 dipeptide in the region between the second and third Ig domain is responsible for virtually all cases of Apert Syndrome (Wilkie, 1995), while paralogous mutations in FGFR1 (S252R) and FGFR3 (P250R) are associated with Pfeiffer and Crouzon syndromes, respectively (Bellus, 1996). FGFR4 is unique in that mutations of this gene are not known to be associated with any developmental disorders.Recently, many of the same activating mutations in the FGFR genes that have been characterized in skeletal and developmental disorders have begun to be identified in a range of cancers (reviewed in Turner and Gross, 2010; Greulich and Pollock, 2011; Wesche, 2011). The best established link between a somatic mutation of an FGFR and the development of cancer is in the case of FGFR3, where 50% of bladder cancers have mutations in the FGFR3 coding sequence. Of these mutations, which largely match the activating mutations seen in thanatophoric dysplasias, over half occur at a single residue (S249C) (Cappellen, 1999; van Rhijn, 2002). Activating mutations have also been identified in the coding sequences of FGFR1, 2 and 4 (for review, see Wesche, 2011)In addition to activating point mutations, the FGFR1, 2 and 3 genes are subject to misregulation in cancer through gene amplification and translocation events, which are thought to lead to overexpression and ligand-independent dimerization (Weiss, 2010; Turner, 2010; Kunii, 2008; Takeda, 2007; Chesi, 1997; Avet-Loiseau, 1998; Ronchetti, 2001). It is important to note, however, that in each of these cases, the amplification or translocation involve large genomic regions encompassing additional genes, and the definitive roles of the FGFR genes in promoting oncogenesis has not been totally established. In the case of FGFR1, translocation events also give rise to FGFR1 fusion proteins that contain the intracellular kinase domain of the receptor fused to a dimerization domain from the partner gene. These fusions, which are expressed in a pre-leukemic myeloproliferative syndrome, dimerize constitutively based on the dimerization domain provided by the fusion partner and are constitutively active (reviewed in Jackson, 2010).

List of identifiers was found at this pathway

P01111	P21802	P01116	O15164	P40763	P42336
P27986	P42224	P11274	P11362		

Authors

Rothfels, K, 2011-03-08

Editors

Weiser, JD

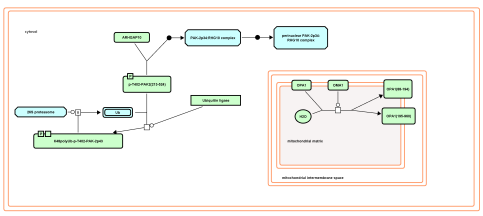
Reviewers

Ezzat, S, 2012-05-15

References

"Graded activation of fibroblast growth factor receptor 3 by mutations causing achondroplasia and thanatophoric dysplasia",Nat Genet,13,1996,233-7.

2.10. Disease (R-HSA-1643685)



Summation

species name:Homo sapiens,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.

List of identifiers was found at this pathway

P09958	P01111	P04626	P01116	P37173	P27986
P21860	Q00987	P42345	P42224	P46940	P21802
P40763	P60484	P49815	P35568	Q06124	P55211
P16234	P11274	P07900	O15528	P00533	O15164
P02751	P21675	P42336	P40692	P46531	P22681
P82987	Q15465	P10721	P11168	P09619	Q09472
P11362	P02788	Q9UHW9	Q13485	P20810	Q7Z5R6
Q14738	P35222	O43524	P98177	P05106	Q969H0
P52292	P08581	Q99758	P54278	P78504	

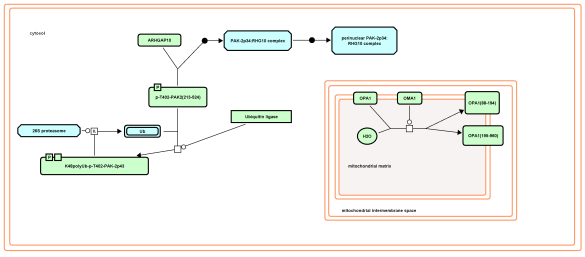
Authors

Matthews, L, 2011-10-11

Editors

Varusai, Thawfeek, 2017-07-25

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



Summation

species name:Homo sapiens,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 hematopoetic 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 lackig 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.

List of identifiers was found at this pathway

P01111	O14757	P17252	P07948	Q06124	P10721
P01116	P40763	P42336	P27986	P22681	P42224
O15524					

Authors

Garapati, P V, 2011-07-11

Editors

Schmidt, Esther

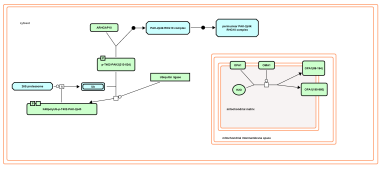
Reviewers

Rönnstrand, L, 2011-08-22

References

"Stem cell factor and its receptor c-Kit as targets for inflammatory diseases",Eur J Pharmacol,533,2006,327-40.

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



Summation

species name:Homo sapiens,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).

List of identifiers was found at this pathway

P09619	P04626	P21802	P10721	P21860	P27986
P35568	Q06124	P16234	P11362	P00533	P08581
P42336					

Authors

Orlic-Milacic, M, 2012-05-01

Editors

Croft, D

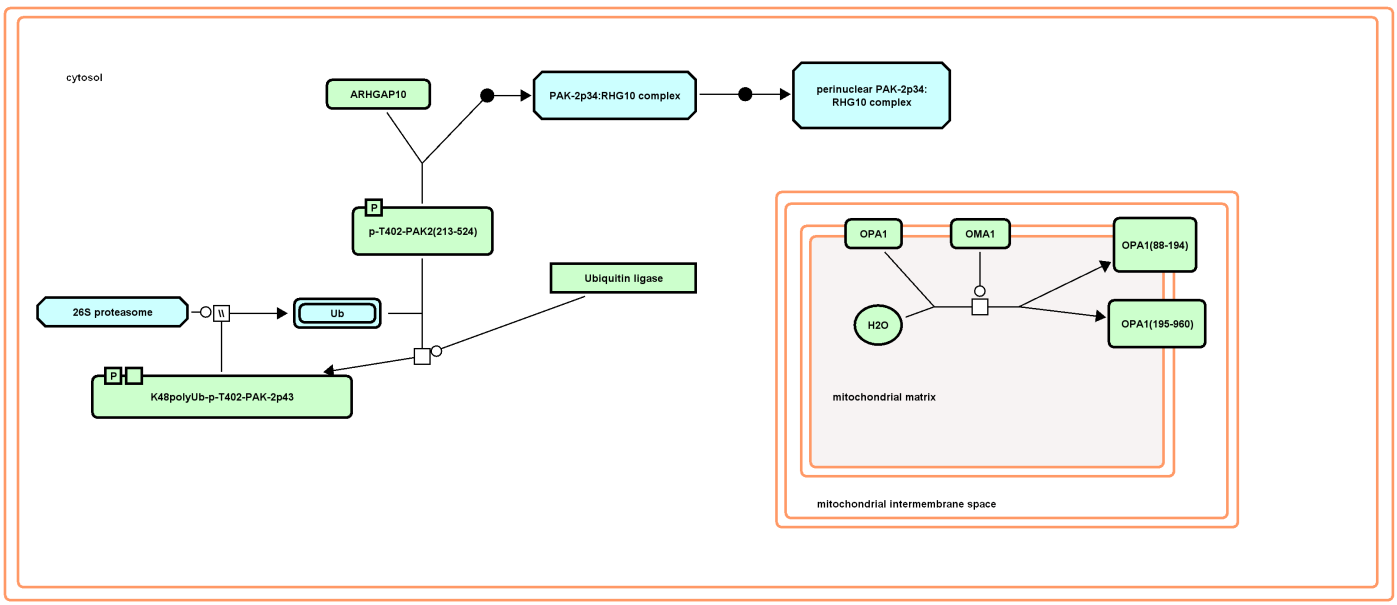
Reviewers

Thorpe, Lauren, 2012-08-13

References

"The structure of a human p110alpha/p85alpha complex elucidates the effects of oncogenic PI3Kalpha mutations",Science,318,2007,1744-8.

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



Summation

species name:Homo sapiens,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; 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.

List of identifiers was found at this pathway

P01111	P56945	P01116	P27986	P42345	P05771
P17948	Q05513	Q05655	P07900	P17252	P35222
P35916	P05106	O15264	P29474	P42336	Q14185
P52735					

Authors

Gopinathrao, G, 2007-03-08 15:44:44

Editors

Schmidt, Esther

Reviewers

Claesson-Welsh, L, 2008-02-28 00:15:17

References

"Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis",J Clin Oncol,23,2005,1011-27.

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

Summation

species name:Homo sapiens,compartment name: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).

List of identifiers was found at this pathway

P01111	P56945	P01116	P27986	P42345	P05771
Q05513	Q05655	P07900	P17252	P35222	P05106
O15264	P29474	P42336	Q14185	P52735	

Authors

Garapati, P V, 2013-08-30

Editors

Schmidt, Esther

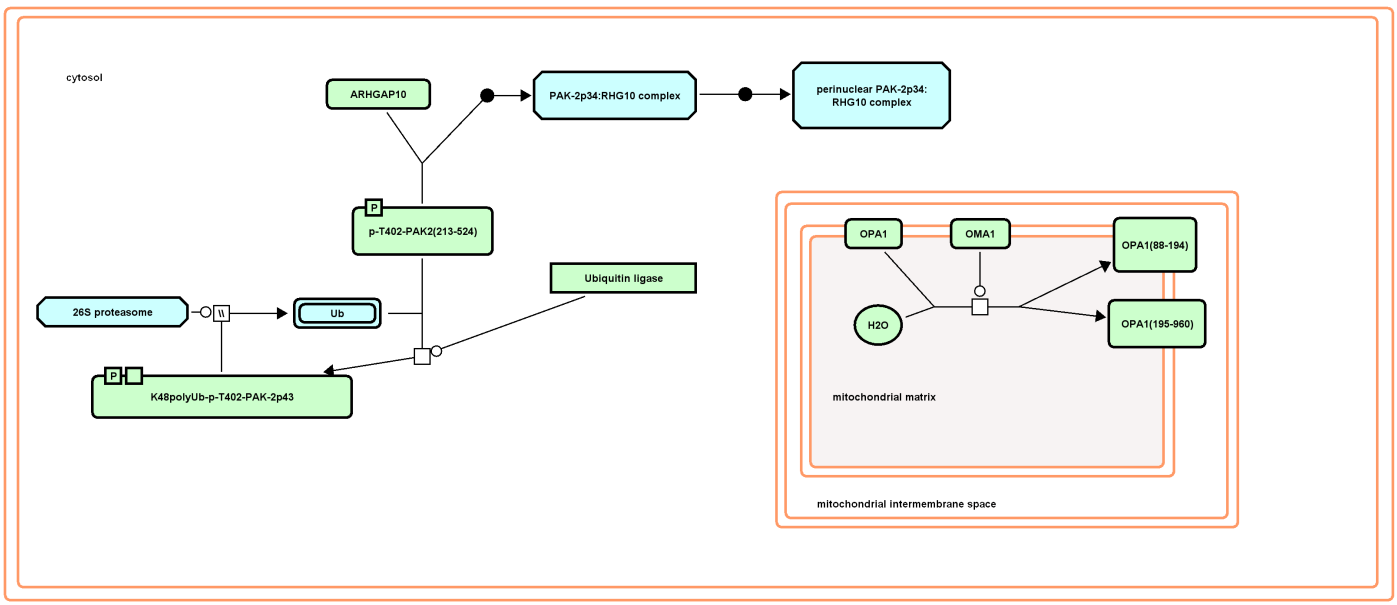
Reviewers

Welsh, Michael, Berger, Philipp, Ballmer-Hofer, Kurt, 2014-05-12

References

"VEGFs and receptors involved in angiogenesis versus lymphangiogenesis",Curr. Opin. Cell Biol.,21,2009,154-65.

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



Summation

species name:Homo sapiens,compartment name: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.

List of identifiers was found at this pathway

P01111	P21802	Q06124	P01116	P42336	P27986
P06213	P35568	P11362			

Authors

Bevan, AP, 2003-07-31 08:01:55

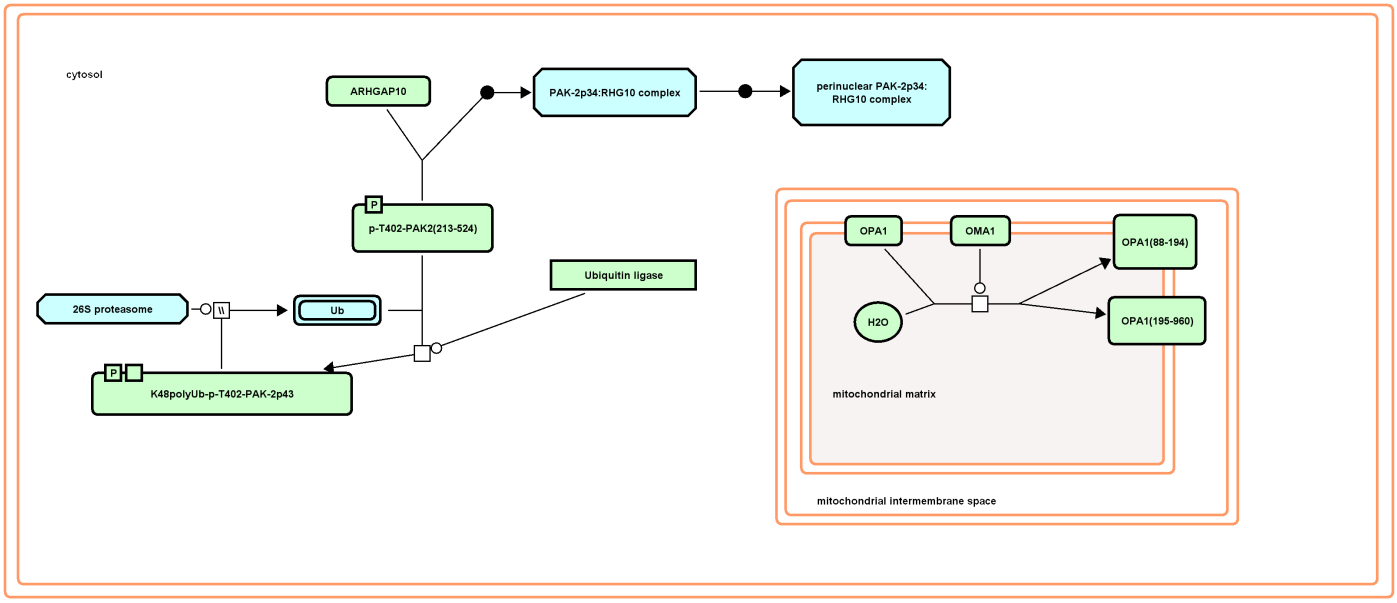
Editors

Croft, D

References

"Phosphoinositide 3-kinase: the key switch mechanism in insulin signalling.",Biochem J,333,1998,471-90.

2.16. Signaling by PDGF (R-HSA-186797)



Summation

species name:Homo sapiens,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.

List of identifiers was found at this pathway

P09958	P01111	P09619	P56945	Q06124	P01116
P40763	P42336	P27986	P42224	P02461	P16234
P12110					

Authors

Jassal, B, 2006-08-15 13:51:10

Editors

Croft, D

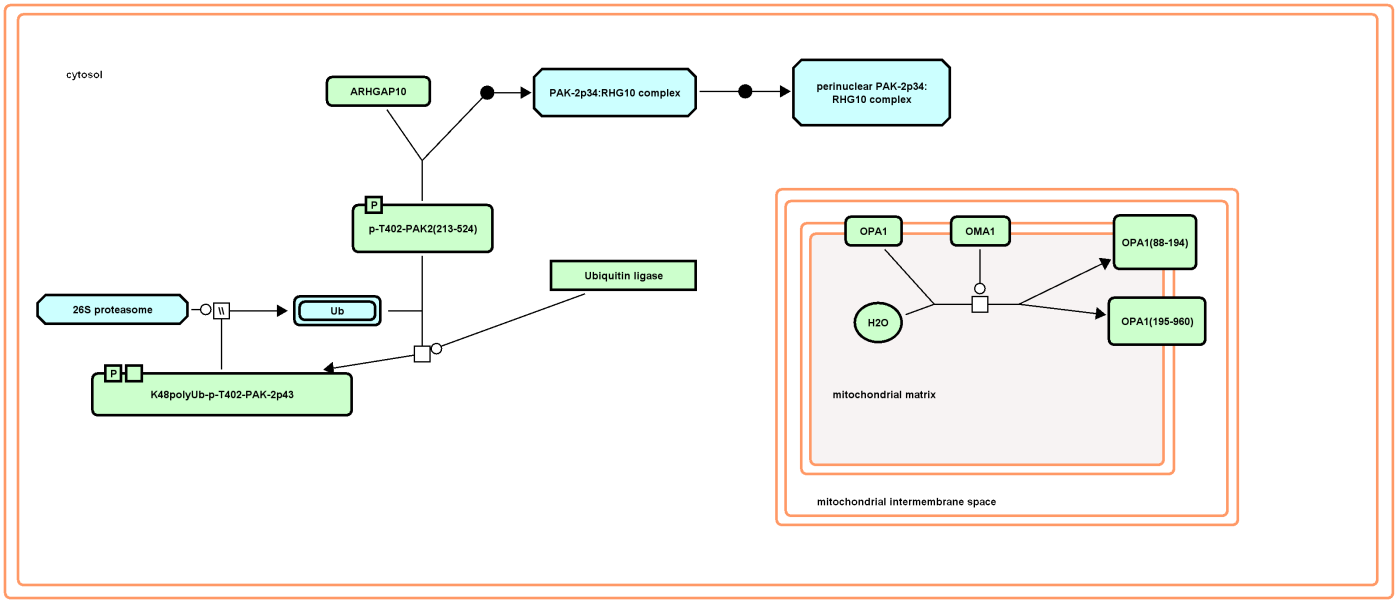
Reviewers

Heldin, CH, 2008-11-23 19:29:34

References

"Signal transduction via platelet-derived growth factor receptors",Biochim Biophys Acta,1378,1998,F79-113.

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



Summation

species name:Homo sapiens,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-lumenal 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.

List of identifiers was found at this pathway

P01111	P21802	Q06124	P01116	P42336	P27986
P06213	P35568	P11362	P36543		

Authors

Bevan, AP, 2003-07-31 08:01:55

Editors

Croft, D

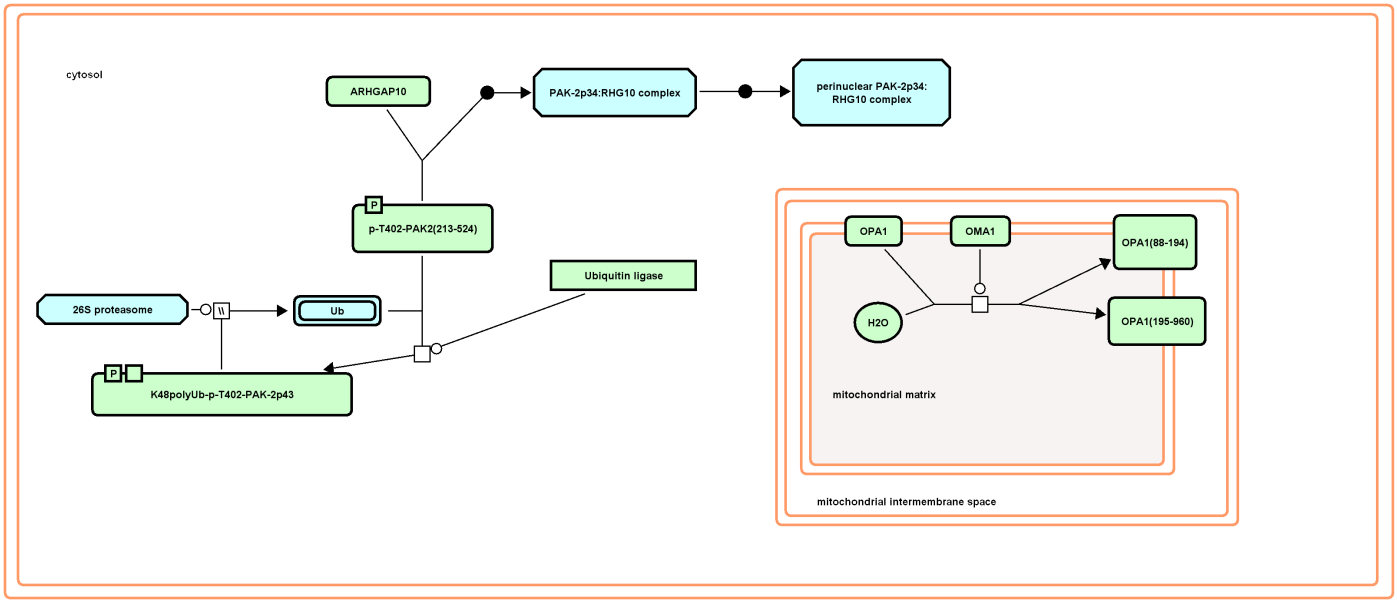
Reviewers

Barroso, I, Stanley, FM, 0000-00-00 00:00:00

References

"The insulin signaling system.",J Biol Chem,269,1994,1-4.

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



Summation

species name:Homo sapiens,compartment name:cytosol,Release of phospho-IRS from the insulin receptor triggers a cascade of signalling events via PI3K, SOS, RAF and the MAP

kinases.

List of identifiers was found at this pathway

P01111	P21802	Q06124	P01116	P42336	P27986
P35568	P11362				

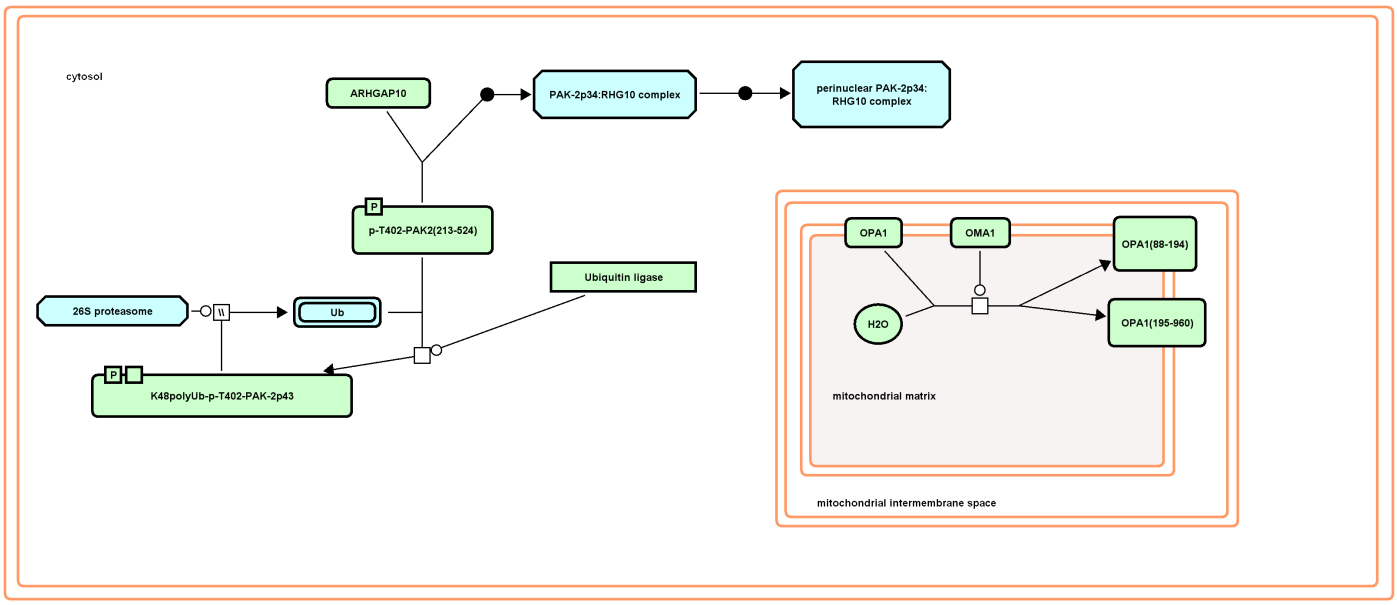
Authors

Charalambous, M, 2004-04-29 09:21:24

Editors

Schmidt, Esther

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



Summation

species name:Homo sapiens,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 survivial, 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).

List of identifiers was found at this pathway

P01111	P09619	P04626	P21802	P10721	P01116
P21860	P46940	P35568	Q06124	Q7Z5R6	Q14738
P16234	P11362	P05106	P02751	P00533	P08581

Authors

Rothfels, Karen, 2015-03-24

Editors

Schmidt, Esther

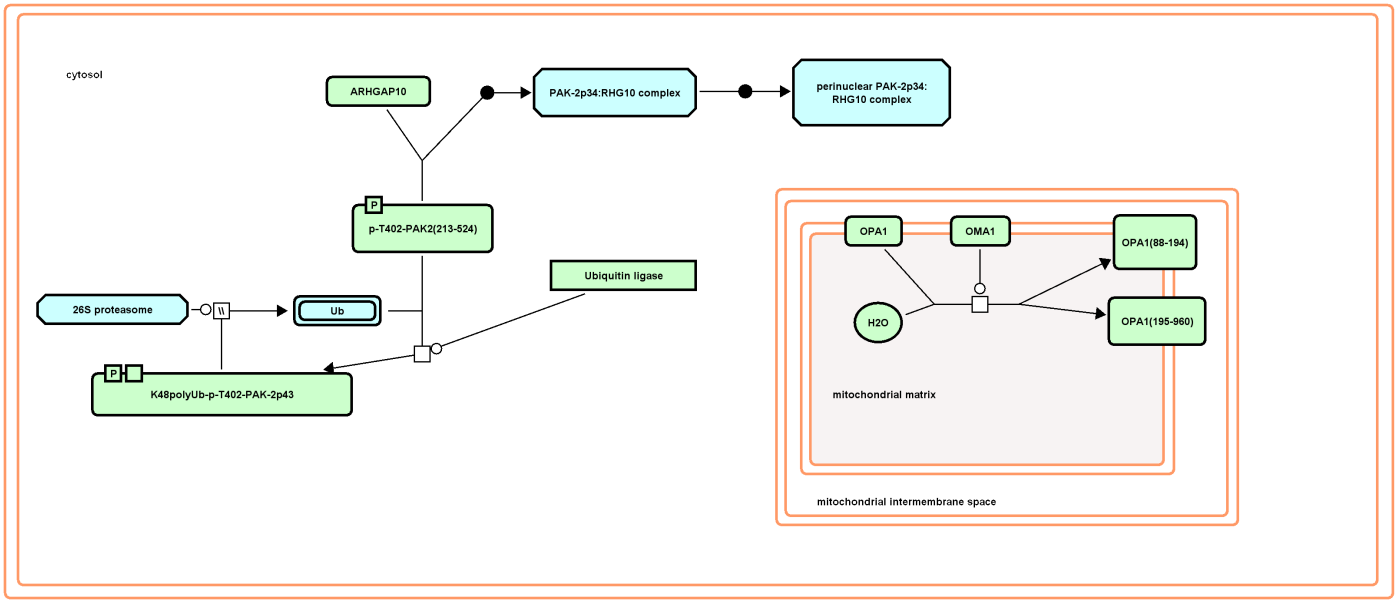
Reviewers

Roskoski, Robert Jr, 2015-04-28

References

"A non-canonical MEK/ERK signaling pathway regulates autophagy via regulating Beclin 1",J. Biol. Chem.,284,2009,21412-24.

2.20. Downstream signal transduction (R-HSA-186763)



Summation

species name:Homo sapiens,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 dowstream 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.

List of identifiers was found at this pathway

P01111	P09619	P56945	Q06124	P01116	P40763
P42336	P27986	P42224	P16234		

Authors

Jassal, B, 2006-08-15 13:51:10

Editors

Croft, D

Reviewers

Heldin, CH, 2008-11-23 19:29:34

References

"Signal transduction via platelet-derived growth factor receptors",Biochim Biophys Acta,1378,1998,F79-113.

3. Identifiers was found.

Identifiers	mapsTo	Resource	Identifiers	mapsTo	Resource
P51587	P51587	UNIPROT	P37275	P37275	UNIPROT
P28329	P28329	UNIPROT	Q06124	Q06124	UNIPROT
P20810	P20810	UNIPROT	Q96GD4	Q96GD4	UNIPROT
O14746	O14746	UNIPROT	P09619	P09619	UNIPROT
O14757	O14757	UNIPROT	Q96L34	Q96L34	UNIPROT
Q6NUQ1	Q6NUQ1	UNIPROT	P28336	P28336	UNIPROT
Q9C040	Q9C040	UNIPROT	P40692	P40692	UNIPROT
O00300	O00300	UNIPROT	Q14185	Q14185	UNIPROT
Q99758	Q99758	UNIPROT	Q09472	Q09472	UNIPROT
P11274	P11274	UNIPROT	P01011	P01011	UNIPROT
P35222	P35222	UNIPROT	Q01974	Q01974	UNIPROT
P60484	P60484	UNIPROT	O43474	O43474	UNIPROT
P49454	P49454	UNIPROT	O00750	O00750	UNIPROT
P01023	P01023	UNIPROT	P49674	P49674	UNIPROT
O00533	O00533	UNIPROT	Q9UPN9	Q9UPN9	UNIPROT
O75382	O75382	UNIPROT	P49815	P49815	UNIPROT
Q13126	Q13126	UNIPROT	P04921	P04921	UNIPROT
P46531	P46531	UNIPROT	P00533	P00533	UNIPROT
Q9HAU5	Q9HAU5	UNIPROT	Q9UNL4	Q9UNL4	UNIPROT
Q13145	Q13145	UNIPROT	P63092	P63092, Q5JWF2	UNIPROT
P36543	P36543	UNIPROT	P49619	P49619	UNIPROT
Q13164	Q13164	UNIPROT	O43524	O43524	UNIPROT
P12110	P12110	UNIPROT	P63096	P63096	UNIPROT
P00338	P00338	UNIPROT	P02751	P02751	UNIPROT
P98177	P98177-1, P98177-2	UNIPROT	Q15119	Q15119	UNIPROT
O15066	O15066	UNIPROT	P02788	P02788	UNIPROT
Q96L91	Q96L91	UNIPROT	P42345	P42345	UNIPROT

Identifiers	mapsTo	Resource	Identifiers	mapsTo	Resource
P04083	P04083	UNIPROT	P08684	P08684	UNIPROT
P46940	P46940	UNIPROT	Q92574	Q92574	UNIPROT
P09544	P09544	UNIPROT	P42336	P42336	UNIPROT
O15264	O15264	UNIPROT	Q13535	Q13535	UNIPROT
P29590	P29590	UNIPROT	P21860	P21860-1	UNIPROT
P55211	P55211	UNIPROT	Q13315	Q13315	UNIPROT
P78504	P78504	UNIPROT	O15439	O15439	UNIPROT
Q05513	Q05513	UNIPROT	P78527	P78527	UNIPROT
Q9Y4A5	Q9Y4A5	UNIPROT	P21675	P21675	UNIPROT
Q99490	Q99490	UNIPROT	P21802	P21802, P21802-18, P21802-1, P21802-17, P21802-5, P21802-3	UNIPROT
Q9UJS0	Q9UJS0	UNIPROT	P16234	P16234	UNIPROT
O15528	O15528	UNIPROT	O15524	O15524	UNIPROT
Q9NRY4	Q9NRY4	UNIPROT	O14686	O14686	UNIPROT
P06400	P06400	UNIPROT	Q8WYB5	Q8WYB5	UNIPROT
P56945	P56945	UNIPROT	P10721	P10721	UNIPROT
Q9BZL6	Q9BZL6	UNIPROT	P16035	P16035	UNIPROT
P42771	Q8N726	UNIPROT	P05106	P05106	UNIPROT
P05107	P05107	UNIPROT	O43184	O43184	UNIPROT
P09958	P09958	UNIPROT	Q7Z5R6	Q7Z5R6	UNIPROT
P37173	P37173	UNIPROT	P06213	P06213	UNIPROT
P02452	P02452	UNIPROT	P07900	P07900	UNIPROT
P04637	P04637	UNIPROT	P15529	P15529	UNIPROT
P11168	P11168	UNIPROT	P17948	P17948	UNIPROT
P01116	P01116	UNIPROT	P27986	P27986	UNIPROT
P01111	P01111	UNIPROT	Q9Y561	Q9Y561	UNIPROT
P52735	P52735	UNIPROT	O95299	O95299	UNIPROT
P11387	P11387	UNIPROT	P02461	P02461	UNIPROT
P04626	P04626	UNIPROT	P10071	P10071	UNIPROT
Q969H0	Q969H0-4, Q969H0-1	UNIPROT	P07948	P07948	UNIPROT
P05771	P05771	UNIPROT	P40763	P40763	UNIPROT
O60934	O60934	UNIPROT	Q99435	Q99435	UNIPROT
Q00987	Q00987	UNIPROT	Q9UHD2	Q9UHD2	UNIPROT
P27540	P27540	UNIPROT	Q13485	Q13485	UNIPROT
Q96HY7	Q96HY7	UNIPROT	Q16760	Q16760	UNIPROT
P11309	P11309	UNIPROT	P22681	P22681	UNIPROT

Identifiers	mapsTo	Resource	Identifiers	mapsTo	Resource
P51812	P51812	UNIPROT	Q02548	Q02548	UNIPROT
P08151	P08151	UNIPROT	P09486	P09486	UNIPROT
P23771	P23771	UNIPROT	O15164	O15164	UNIPROT
Q15465	Q15465	UNIPROT	P04843	P04843	UNIPROT
P35568	P35568	UNIPROT	P54278	P54278	UNIPROT
P14859	P14859	UNIPROT	P82987	P82987	UNIPROT
Q9NQC7	Q9NQC7	UNIPROT	Q86UP2	Q86UP2	UNIPROT
P11362	P11362, P11362-19, P11362-1	UNIPROT	Q13635	Q13635	UNIPROT
P42224	P42224	UNIPROT	Q9UHW9	Q9UHW9	UNIPROT
O43602	O43602	UNIPROT	Q14738	Q14738	UNIPROT
Q99081	Q99081	UNIPROT	P52292	P52292	UNIPROT
P09668	P09668	UNIPROT	P29474	P29474	UNIPROT
P35916	P35916	UNIPROT	Q13418	Q13418	UNIPROT
P17252	P17252	UNIPROT	O15151	O15151	UNIPROT
Q03001	Q03001-3	UNIPROT	Q05655	Q05655	UNIPROT
P30291	P30291	UNIPROT	P42262	P42262	UNIPROT
P08123	P08123	UNIPROT	Q13444	Q13444	UNIPROT
Q07812	Q07812	UNIPROT	P10415	P10415	UNIPROT
O60346	O60346	UNIPROT	P08581	P08581	UNIPROT
P24821	P24821	UNIPROT	P45984	P45984	UNIPROT

4. Identifiers was not found.

Identifiers					
O95831	Q8IWV1	Q13214	P35716	O43692	P08922
Q16799	Q8IZT6	Q06455	Q9H0K1	Q9H1R3	Q8TF68
Q9BXK5	Q9NRP7	Q6ZWH5	Q01543	Q92786	P04198
Q32MQ5	P08247				