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This report is intend for reviewer of the pathway analysis:MjAxNzEyMTgwNjM0MDJfMjI%3D (please note that this URL maybe out of date because of the token can expired at our server end) and your input identifiers are :O95831, Q8IWV1, Q13214, P35716, O43692....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 09:12 26-01-2018.

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

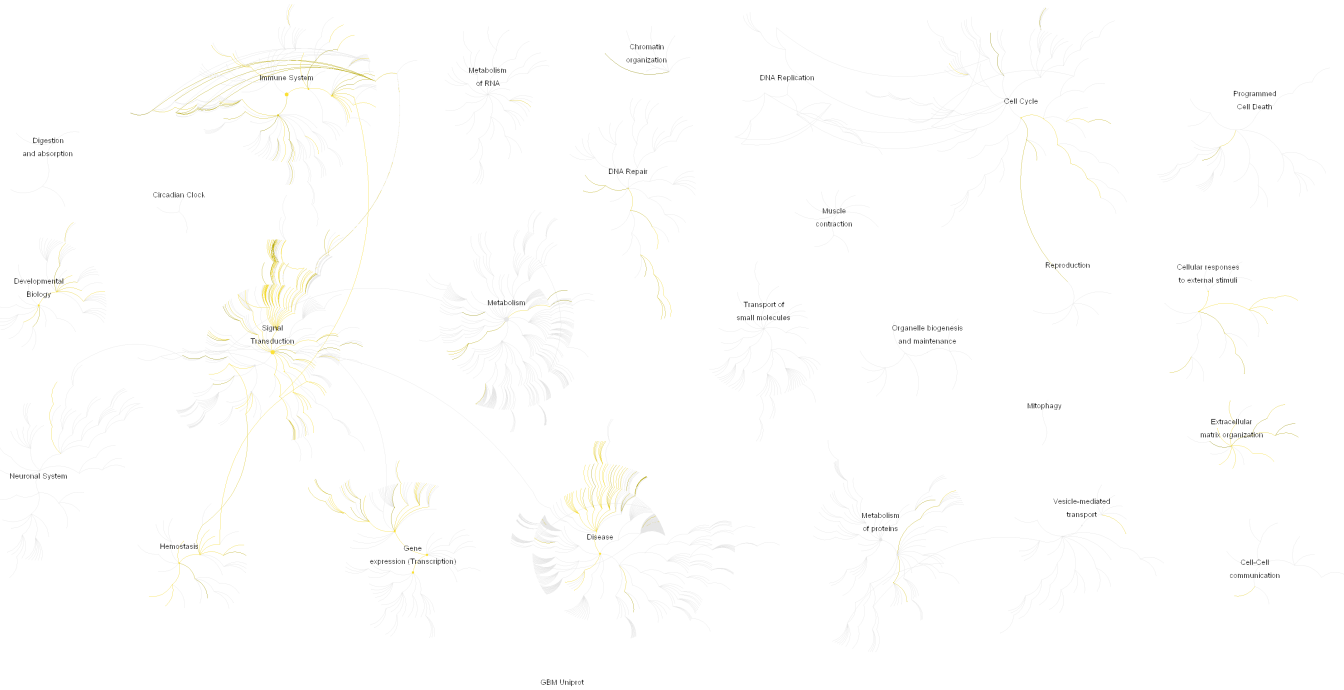
Summary

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

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

3. 50 of top Enhanced/Overrepresented pathways was list based on p-Value.

4. The Pathways Overview diagram for this analysis:



Overview

1. Top 50 Overrepresentation pathways sorted by p-Value.

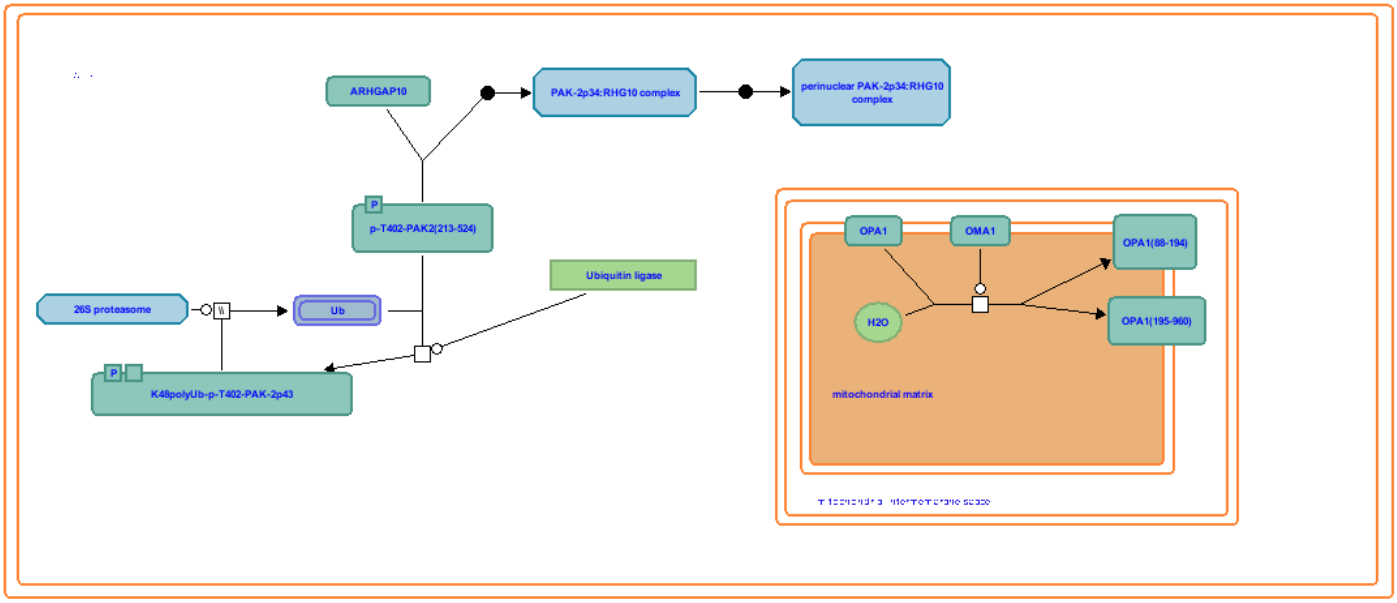
Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total	Reactions ratio	Species name
Diseases of signal transduction	50	467	0.0345	1.11022e-16	2.84217e-14	225	297	0.0265	Homo sapiens
Signaling by Receptor Tyrosine Kinases	53	585	0.0432	1.11022e-16	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

Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total	Reactions ratio	Species name
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
IRS-related events triggered by IGF1R	12	65	0.0048	4.16429e-10	1.91557e-08	6	12	0.0011	Homo sapiens
Signaling by FGFR1 in disease	11	53	0.0039	6.78820e-10	2.89189e-08	35	35	0.0031	Homo sapiens
IGF1R signaling cascade	12	68	0.0050	6.88545e-10	2.89189e-08	7	17	0.0015	Homo sapiens
RAF/MAP kinase cascade	21	267	0.0197	7.83445e-10	3.15859e-08	17	39	0.0035	Homo sapiens
Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R)	12	69	0.0051	8.09896e-10	3.15859e-08	7	19	0.0017	Homo sapiens
MAPK family signaling cascades	23	325	0.0240	8.68407e-10	3.21311e-08	23	86	0.0077	Homo sapiens
Platelet activation, signaling and aggregation	22	305	0.0225	1.46634e-09	5.27882e-08	57	114	0.0102	Homo sapiens
Hemostasis	36	801	0.0591	2.80026e-09	9.80090e-08	88	323	0.0288	Homo sapiens
Signaling by MET	12	87	0.0064	1.03743e-08	3.52727e-07	47	49	0.0044	Homo sapiens
PI3K Cascade	10	55	0.0041	1.41487e-08	4.52758e-07	2	7	0.0006	Homo sapiens
Downstream signaling of activated FGFR2	9	41	0.0030	1.54825e-08	4.79957e-07	23	23	0.0021	Homo sapiens
FGFR1 mutant receptor activation	9	44	0.0032	2.81383e-08	8.44148e-07	25	25	0.0022	Homo sapiens
Signaling by FGFR2 in disease	10	61	0.0045	3.69058e-08	1.07027e-06	27	28	0.0025	Homo sapiens
Signaling by FGFR	12	106	0.0078	8.69654e-08	2.27109e-06	93	142	0.0127	Homo sapiens
Signaling by ERBB2	10	67	0.0049	8.73498e-08	2.27109e-06	38	43	0.0038	Homo sapiens
Signaling by PTK6	10	67	0.0049	8.73498e-08	2.27109e-06	26	52	0.0046	Homo sapiens
Signaling by Non-Receptor Tyrosine Kinases	10	67	0.0049	8.73498e-08	2.27109e-06	26	52	0.0046	Homo sapiens
Interleukin-4 and 13 signaling	16	212	0.0156	1.53936e-07	3.84841e-06	24	46	0.0041	Homo sapiens
Signaling by EGFRvIII in Cancer	7	26	0.0019	1.63399e-07	3.92156e-06	18	18	0.0016	Homo sapiens
Constitutive Signaling by EGFRvIII	7	26	0.0019	1.63399e-07	3.92156e-06	18	18	0.0016	Homo sapiens
Syndecan interactions	7	29	0.0021	3.38039e-07	7.77489e-06	6	15	0.0013	Homo sapiens
Signaling by Interleukins	28	642	0.0474	3.68035e-07	8.46480e-06	127	481	0.0429	Homo sapiens
PI-3K cascade:FGFR2	7	31	0.0023	5.25872e-07	1.15692e-05	7	7	0.0006	Homo sapiens
Constitutive Signaling by AKT1 E17K in Cancer	7	32	0.0024	6.48609e-07	1.39525e-05	5	18	0.0016	Homo sapiens
Axon guidance	26	583	0.0430	6.64405e-07	1.39525e-05	57	297	0.0265	Homo sapiens
Cytokine Signaling in Immune system	35	961	0.0709	7.71066e-07	1.58908e-05	163	614	0.0547	Homo sapiens
FRS-mediated FGFR2 signaling	7	33	0.0024	7.94541e-07	1.58908e-05	9	9	0.0008	Homo sapiens

Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total	Reactions ratio	Species name
Signaling by FGFR2	10	87	0.0064	9.22246e-07	1.84449e-05	34	46	0.0041	Homo sapiens
SHC1 events in ERBB2 signaling	7	35	0.0026	1.16996e-06	2.33991e-05	5	6	0.0005	Homo sapiens
NGF signalling via TRKA from the plasma membrane	10	90	0.0066	1.24584e-06	2.36709e-05	16	55	0.0049	Homo sapiens

2. Pathway details.

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



Summation

species name:Homo sapiens,compartment name:plasma membrane,disease name:cancer,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). Many of the resulting mutant FGFR1 proteins can dimerize and promote signaling in a ligand-independent fashion, although signal transduction may still be amplified in the presence of ligand (reviewed in Turner and Gross, 2010; Greulich and Pollock, 2011; Wesche et al, 2011).

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

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Reviewers

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References

Webster MK,Donoghue DJ, "FGFR activation in skeletal disorders: too much of a good thing", Trends Genet, 13, 1997, 178-82.

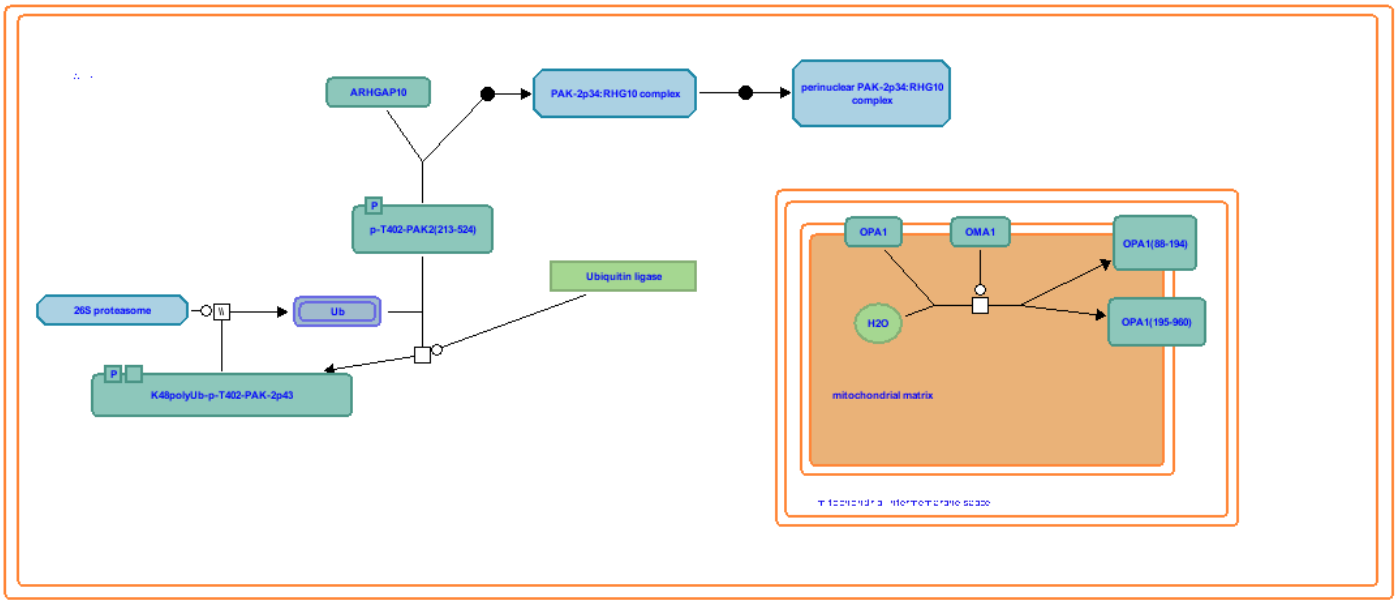
Burke D,Wilkes D,Blundell TL,Malcolm S, "Fibroblast growth factor receptors: lessons from the genes", Trends Biochem Sci, 23, 1998, 59-62.

Cunningham ML,Seto ML,Ratisoontorn C,Heike CL,Hing AV, "Syndromic craniosynostosis: from history to hydrogen bonds", Orthod Craniofac Res, 10, 2007, 67-81.

Wesche J,Haglund K,Haugsten EM, "Fibroblast growth factors and their receptors in cancer", Biochem J, 437, 2011, 199-213.

Turner N,Grose RP, "Fibroblast growth factor signalling: from development to cancer", Nat Rev Cancer, 10, 2010, 116-29.

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



Summation

species name:Homo sapiens,Cytokines are small proteins that regulate and mediate immunity, inflammation, and hematopoiesis. They are secreted in response to immune stimuli, and usually act briefly, locally, at very low concentrations. Cytokines bind to specific membrane receptors, which then signal the cell via second messengers, to regulate cellular activity.

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

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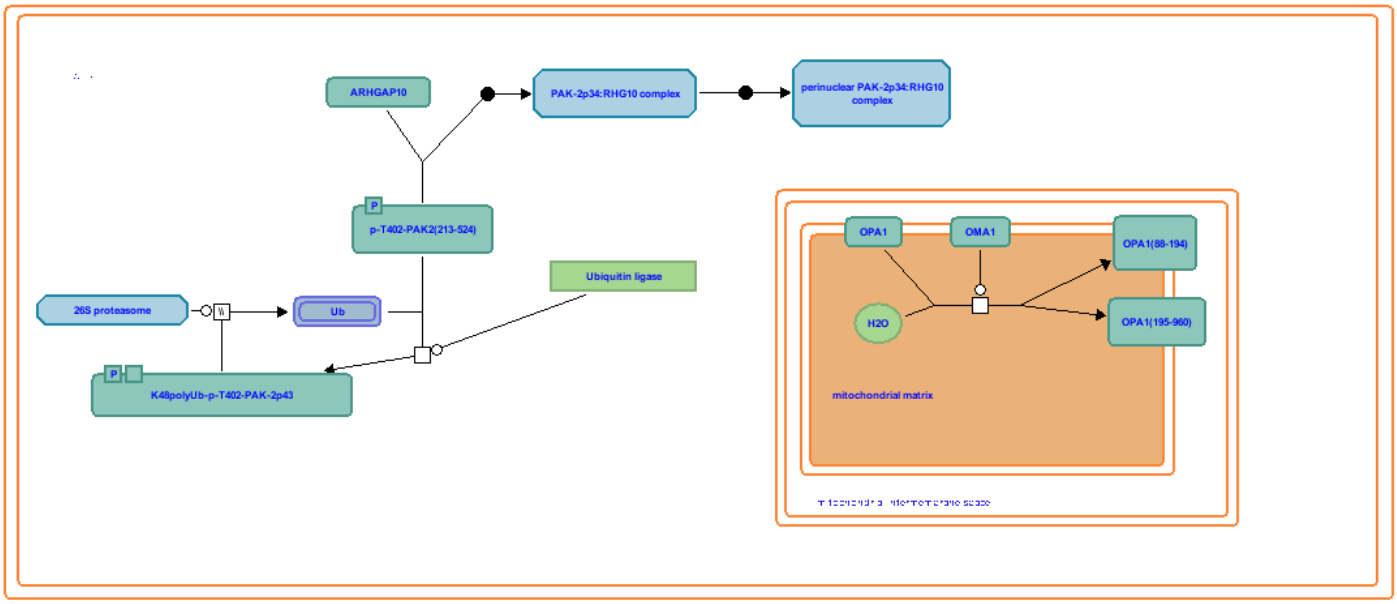
References

Santamaria P, "Cytokines and chemokines in autoimmune disease: an overview", Adv Exp Med Biol, 520, 2003, 1-7.

2.3. Signal Transduction (R-HSA-162582)



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

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

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References

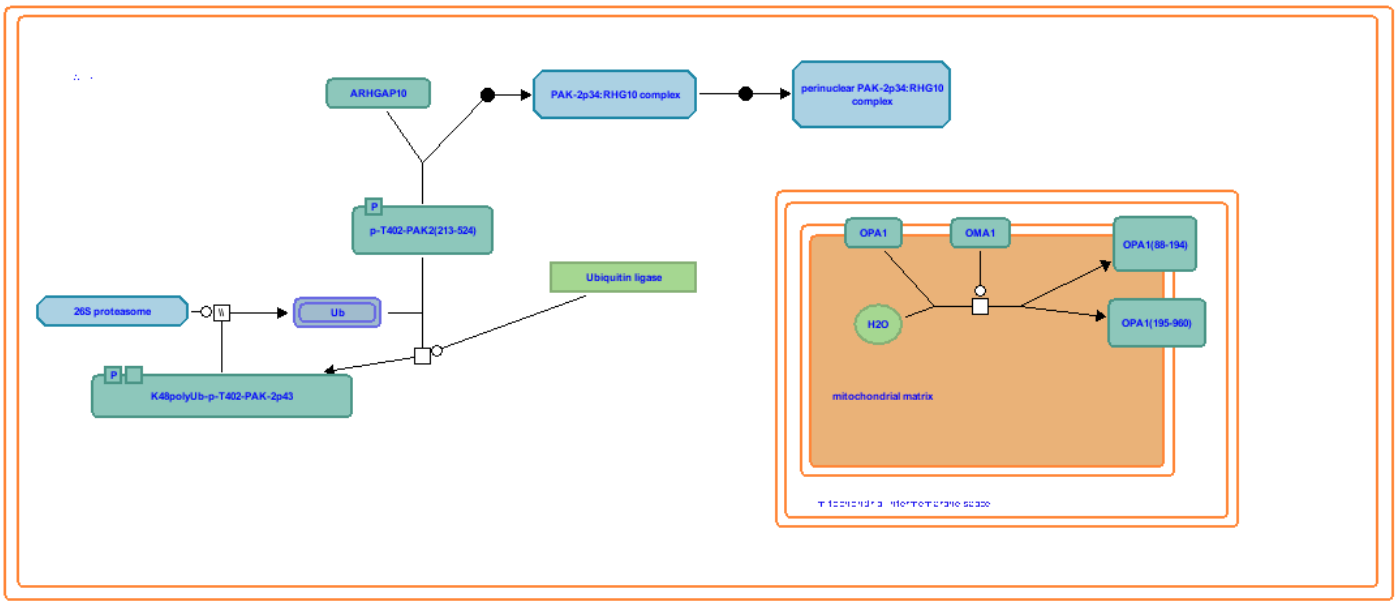
Olsson AK,Dimberg A,Kreuger J,Claesson-Welsh L, "VEGF receptor signalling - in control of vascular function", Nat Rev Mol Cell Biol, 7, 2006, 359-71.

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

Lohela M,Bry M,Tammela T,Alitalo K, "VEGFs and receptors involved in angiogenesis versus lymphangiogenesis", Curr. Opin. Cell Biol., 21, 2009, 154-65.

Otrock ZK,Makarem JA,Shamseddine AI, "Vascular endothelial growth factor family of ligands and receptors: review", Blood Cells Mol. Dis., 38, 2007, 258-68.

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



Summation

species name:Homo sapiens,disease name:cancer,EGFRvIII (EGFR V30_R297delinsG) is the most prevalent EGFR variant in glioblastoma, but it is also found in other cancer types. In-frame deletion of the ligand binding domain in EGFRvIII is frequently accompanied with genomic amplification, resulting in over-expression of EGFRvIII. EGFRvIII dimerizes and autophosphorylates spontaneously and is therefore constitutively active (Fernandes et al. 2001)

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				

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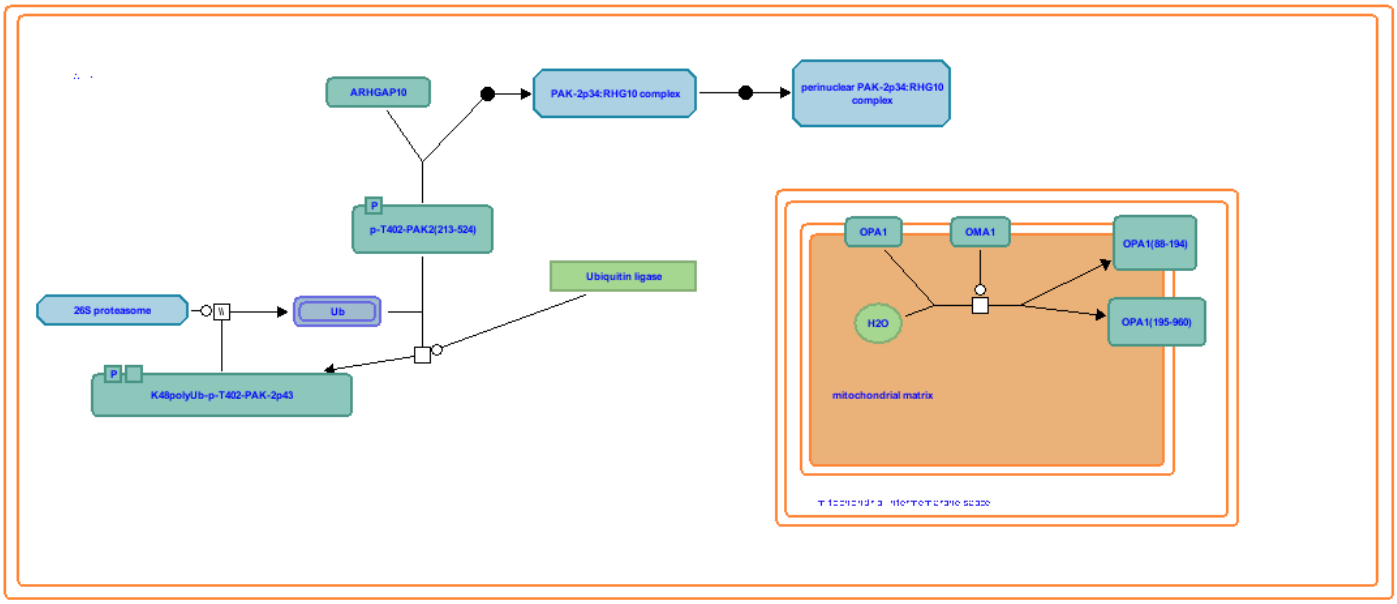
References

Fernandes H,Cohen S,Bishayee S, "Glycosylation-induced conformational modification

positively regulates receptor-receptor association: a study with an aberrant epidermal growth factor receptor (EGFRvIII/DeltaEGFR) expressed in cancer cells", J Biol Chem, 276, 2001, 5375-83.

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



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

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

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Schmidt Esther,017-11-18

References

Edling CE,Hallberg B, "c-Kit--a hematopoietic cell essential receptor tyrosine kinase", Int J Biochem Cell Biol, 39, 2007, 1995-8.

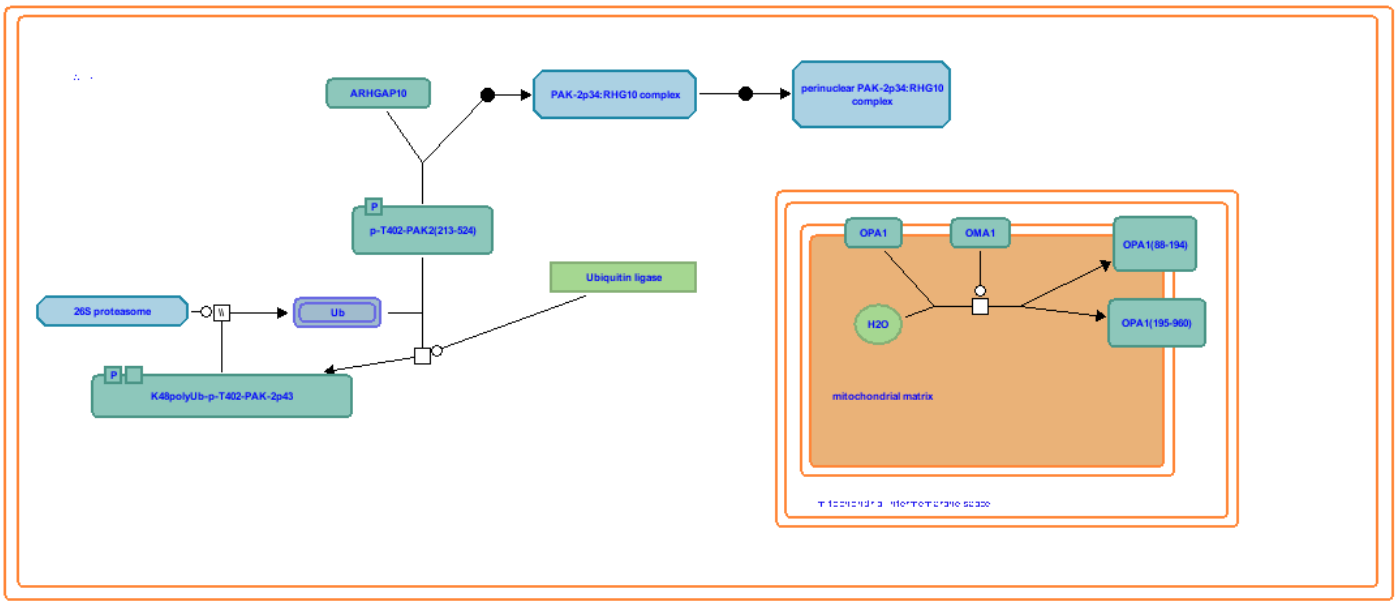
Rönnstrand L, "Signal transduction via the stem cell factor receptor/c-Kit", Cell Mol Life Sci, 61, 2004, 2535-48.

Reber L,Da Silva CA,Frossard N, "Stem cell factor and its receptor c-Kit as targets for inflammatory diseases", Eur J Pharmacol, 533, 2006, 327-40.

Lennartsson J,Rönnstrand L, "The stem cell factor receptor/c-Kit as a drug target in cancer", Curr Cancer Drug Targets, 6, 2006, 65-75.

Masson K,Rönnstrand L, "Oncogenic signaling from the hematopoietic growth factor receptors c-Kit and Flt3", Cell Signal, 21, 2009, 1717-26.

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



Summation

species name:Homo sapiens,disease name:disease,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

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					

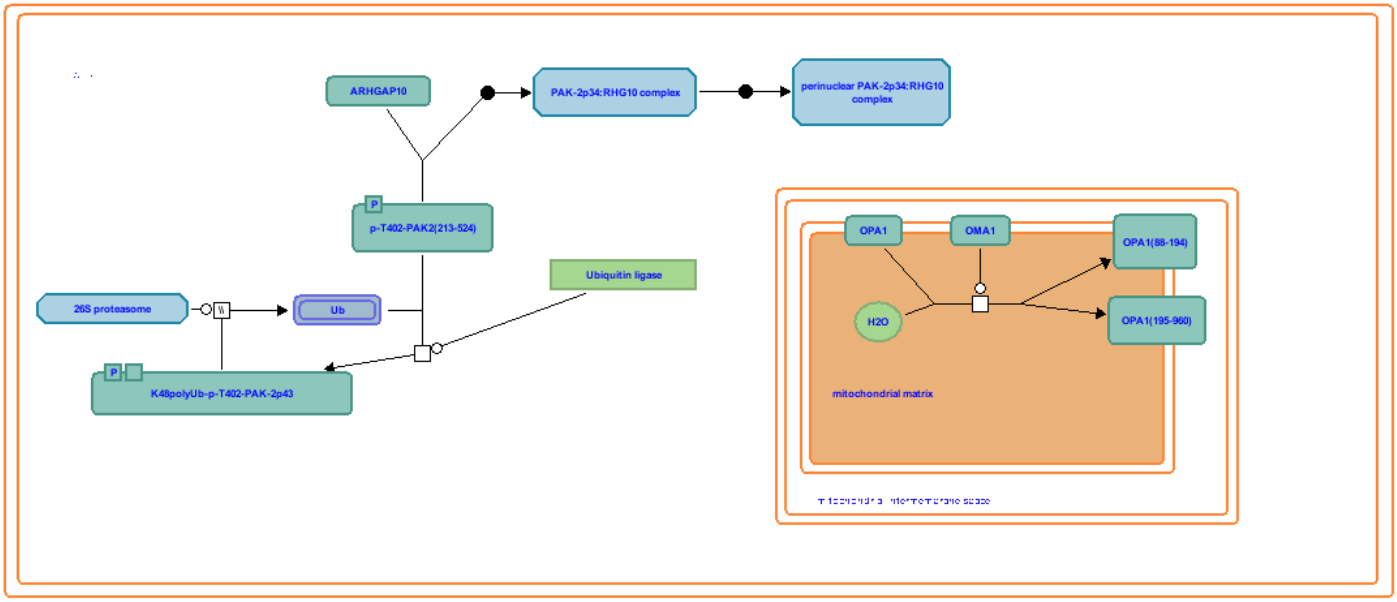
Reviewers

Shorser Solomon,016-11-08

References

Pires-daSilva A,Sommer RJ, "The evolution of signalling pathways in animal development", Nat. Rev. Genet., 4, 2003, 39-49.

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



Summation

species name:Homo sapiens,disease name:bone development disease,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

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

Authors

Rothfels Karen,012-02-10

Editors

Rothfels Karen,012-05-15

Reviewers

Weiser null,016-09-16

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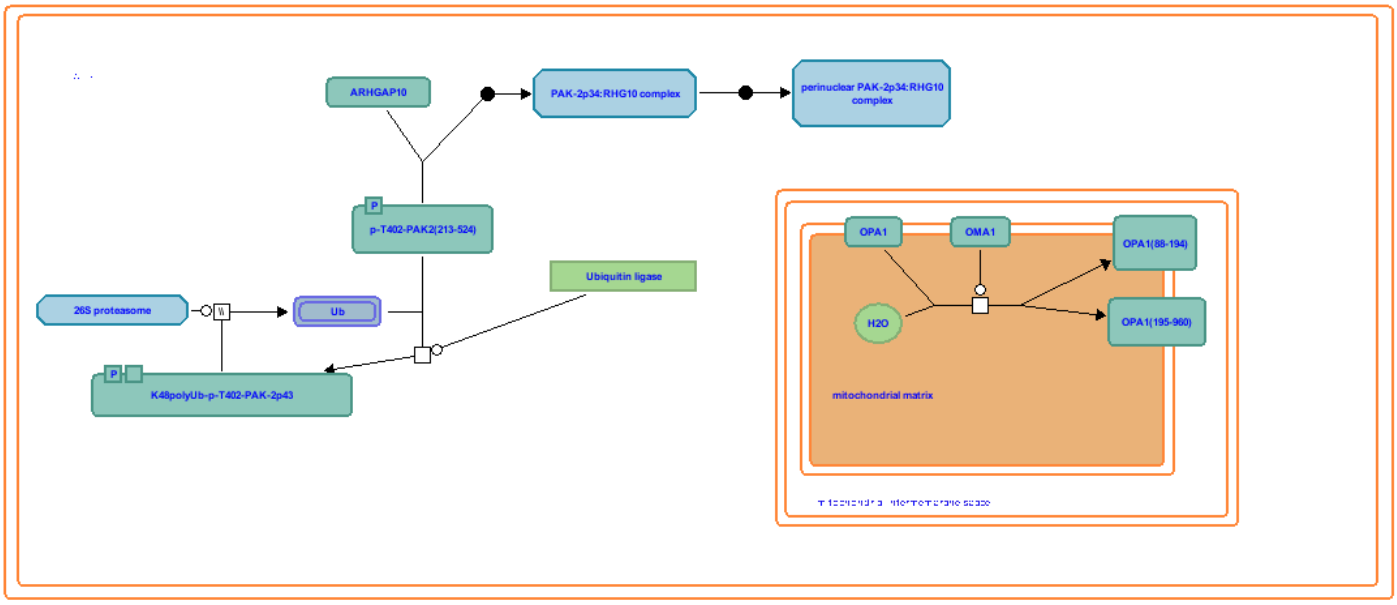
Burke D,Wilkes D,Blundell TL,Malcolm S, "Fibroblast growth factor receptors: lessons from the genes", Trends Biochem Sci, 23, 1998, 59-62.

Cunningham ML,Seto ML,Ratisoontorn C,Heike CL,Hing AV, "Syndromic craniosynostosis: from history to hydrogen bonds", Orthod Craniofac Res, 10, 2007, 67-81.

Harada D,Yamanaka Y,Ueda K,Tanaka H,Seino Y, "FGFR3-related dwarfism and cell signaling", J Bone Miner Metab, 27, 2009, 9-15.

Galvin BD,Hart KC,Meyer AN,Webster MK,Donoghue DJ, "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.

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



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

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

P00533 P08581 P42336

Authors

Rothfels Karen,017-05-24

Editors

Rothfels Karen,017-05-24

Reviewers

Schmidt Esther,017-11-18

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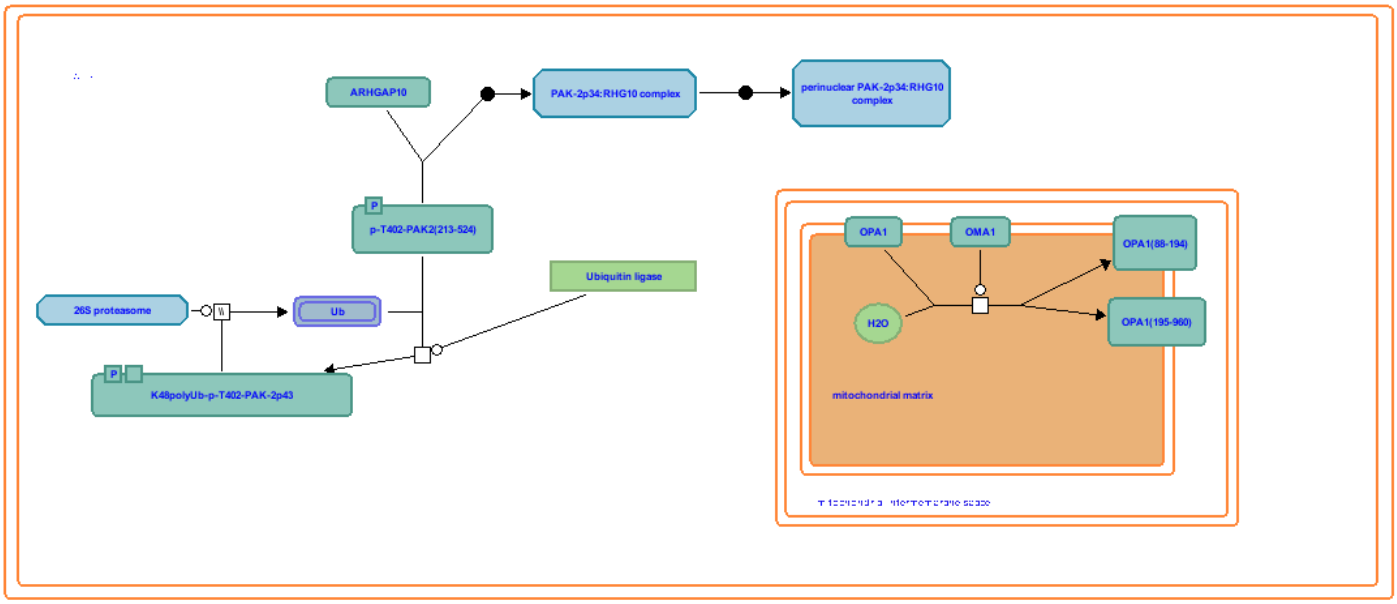
Wellbrock C,Karasarides M,Marais R, "The RAF proteins take centre stage", Nat Rev Mol Cell Biol, 5, 2004, 875-85.

Manning BD,Cantley LC, "AKT/PKB signaling: navigating downstream", Cell, 129, 2007, 1261-74.

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

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



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 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).

List of identifiers was found at this pathway

P01111	P21802	P01116	O15164	P40763	P42336
P27986	P42224	P11274	P11362		

Authors

Rothfels Karen,015-03-11

Reviewers

Schmidt Esther,017-11-18

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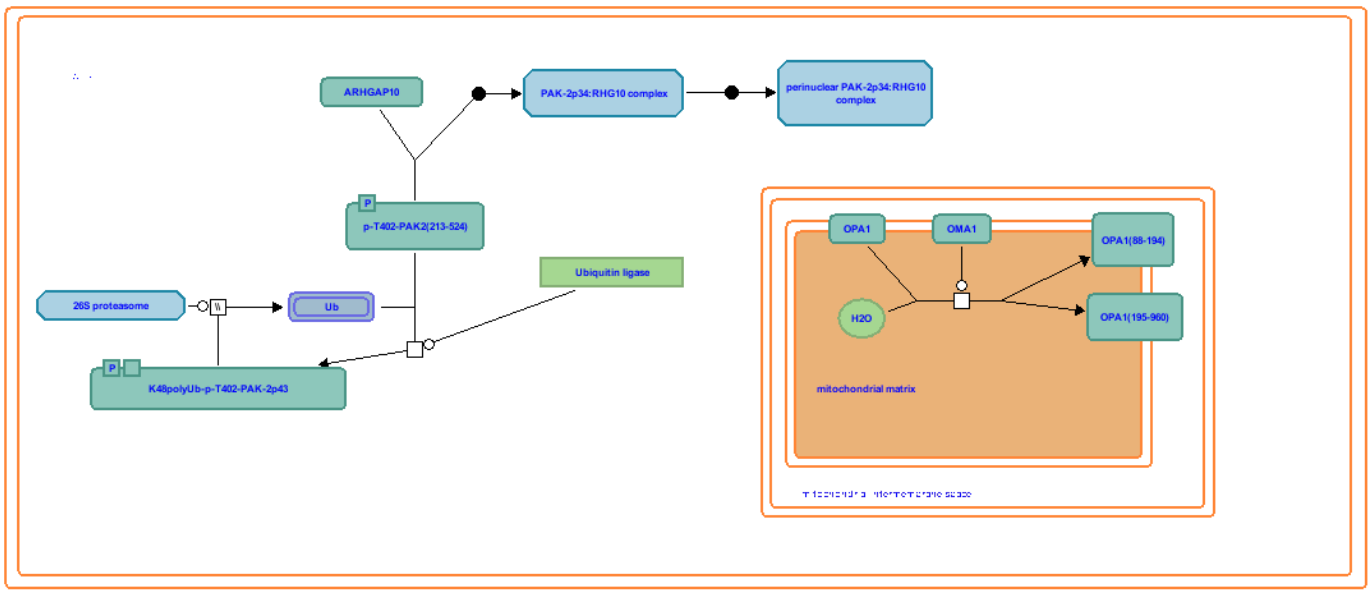
Raman M,Chen W,Cobb MH, "Differential regulation and properties of MAPKs", Oncogene, 26, 2007, 3100-12.

Matallanas D,Birtwistle M,Romano D,Zebisch A,Rauch J,von Kriegsheim A,Kolch W, "Raf family kinases: old dogs have learned new tricks", Genes Cancer, 2, 2011, 232-60.

Wellbrock C,Karasarides M,Marais R, "The RAF proteins take centre stage", Nat Rev Mol Cell Biol, 5, 2004, 875-85.

2.10. Disease (R-HSA-1643685)



Summation

species name:Homo sapiens,Trk receptors signal from the plasma membrane and from intracellular membranes, particularly from early endosomes. Signalling from the plasma membrane is fast but transient; signalling from endosomes is slower but long lasting. Signalling from the plasma membrane is annotated here. TRK signalling leads to proliferation in some cell types and neuronal differentiation in others. Proliferation is the likely outcome of short term signalling, as observed following stimulation of EGFR (EGF receptor). Long term signalling via TRK receptors, instead, was clearly shown to be required for neuronal differentiation in response to neurotrophins.

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

Nasi null,006-10-10Annibali null,006-10-10

Editors

Jassal Bijay,006-10-10

Reviewers

Schmidt Esther,017-11-18

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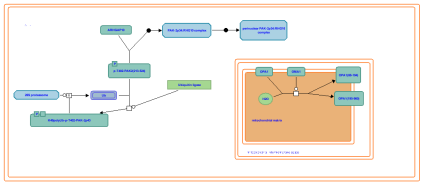
Kaplan DR,Miller FD, "Neurotrophin signal transduction in the nervous system", Curr Opin Neurobiol, 10, 2000, 381-91.

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



Summation

species name:Homo sapiens,The FRS family of scaffolding adaptor proteins has two members, FRS2 (also known as FRS2 alpha) and FRS3 (also known as FRS2beta or SNT-2). Activation of FGFR tyrosine kinase allows FRS proteins to become phosphorylated on tyrosine residues and then bind to the adaptor GRB2 and the tyrosine phosphatase PPTN11/SHP2. Subsequently, PPTN11 activates the RAS-MAP kinase pathway and GRB2 activates the RAS-MAP kinase , PI-3-kinase and ubiquitinations/degradation pathways by binding to SOS, GAB1 and CBL, respectively, via the SH3 domains of GRB2. FRS2 acts as a central mediator in FGF signaling mainly because it induces sustained levels of activation of ERK with ubiquitous expression.

List of identifiers was found at this pathway

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

Authors

de Bono Bernard,007-01-10

Editors

Jupe Steve,010-02-03

Reviewers

Schmidt Esther,017-11-18

References

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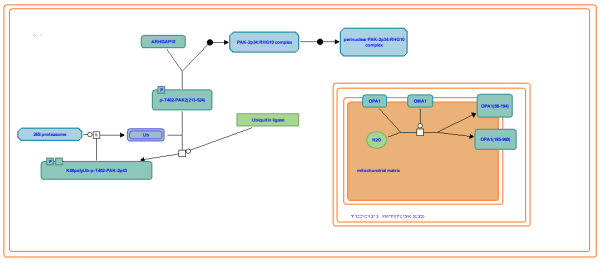
Manuvakhova M,Thottassery JV,Hays S,Qu Z,Rentz SS,Westbrook L,Kern FG, "Expression of the SNT-1/FRS2 phosphotyrosine binding domain inhibits activation of MAP kinase and PI3-kinase pathways and antiestrogen resistant growth induced by FGF-1 in human breast carcinoma cells", Oncogene, 25, 2006, 6003-14.

Gotoh N, "Regulation of growth factor signaling by FRS2 family docking/scaffold adaptor proteins", Cancer Sci, 99, 2008, 1319-25.

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



Summation

species name:Homo sapiens,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 phophorylate 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 relocalizes to the nucleus in response to stimuli (reviewed in Roskoski 2012b; Turjanski et al, 2007; Plotnikov et al, 2010; Cargnello 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).

List of identifiers was found at this pathway

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

Authors

Rothfels Karen,015-02-12

Editors

Rothfels Karen,015-02-12

Reviewers

Croft David,017-12-04

References

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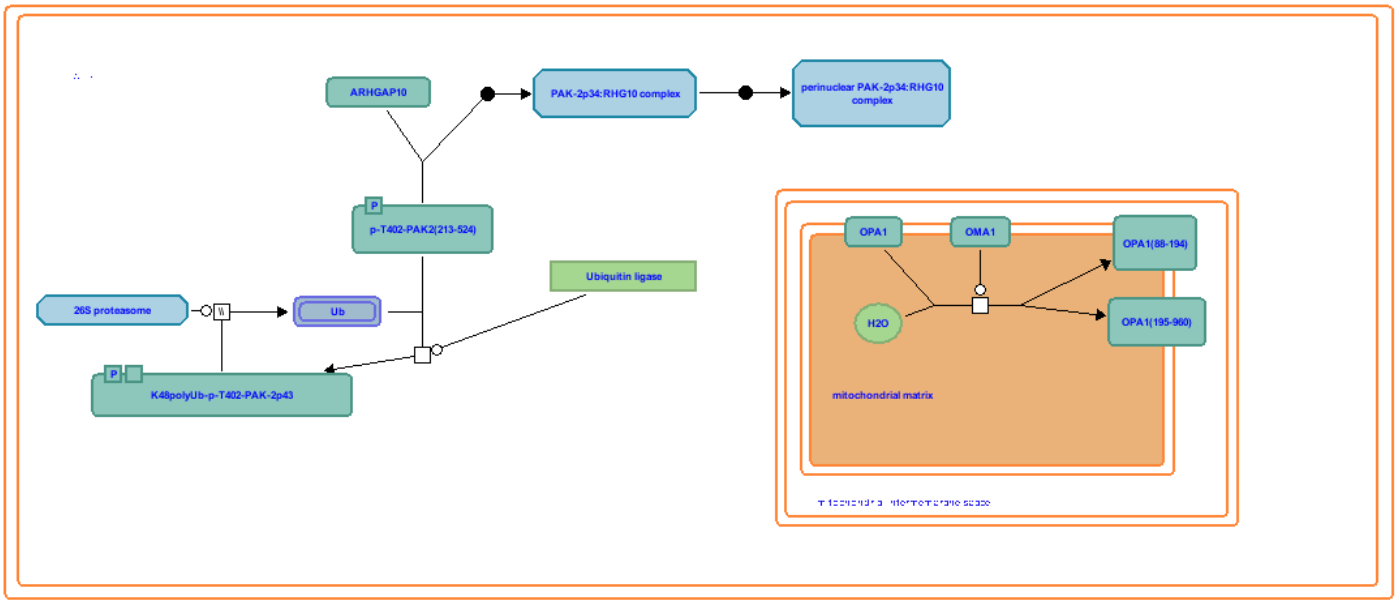
Wellbrock C,Karasarides M,Marais R, "The RAF proteins take centre stage", Nat Rev Mol Cell Biol, 5, 2004, 875-85.

Roskoski R Jr, "ERK1/2 MAP kinases: structure, function, and regulation", Pharmacol. Res., 66, 2012, 105-43.

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



Summation

species name:Homo sapiens,disease name:cancer,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 (Ibrahimi, 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 analagous 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).

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

Rothfels Karen,014-11-20

Editors

Rothfels Karen,014-12-05

Reviewers

Rothfels Karen,016-01-22

References

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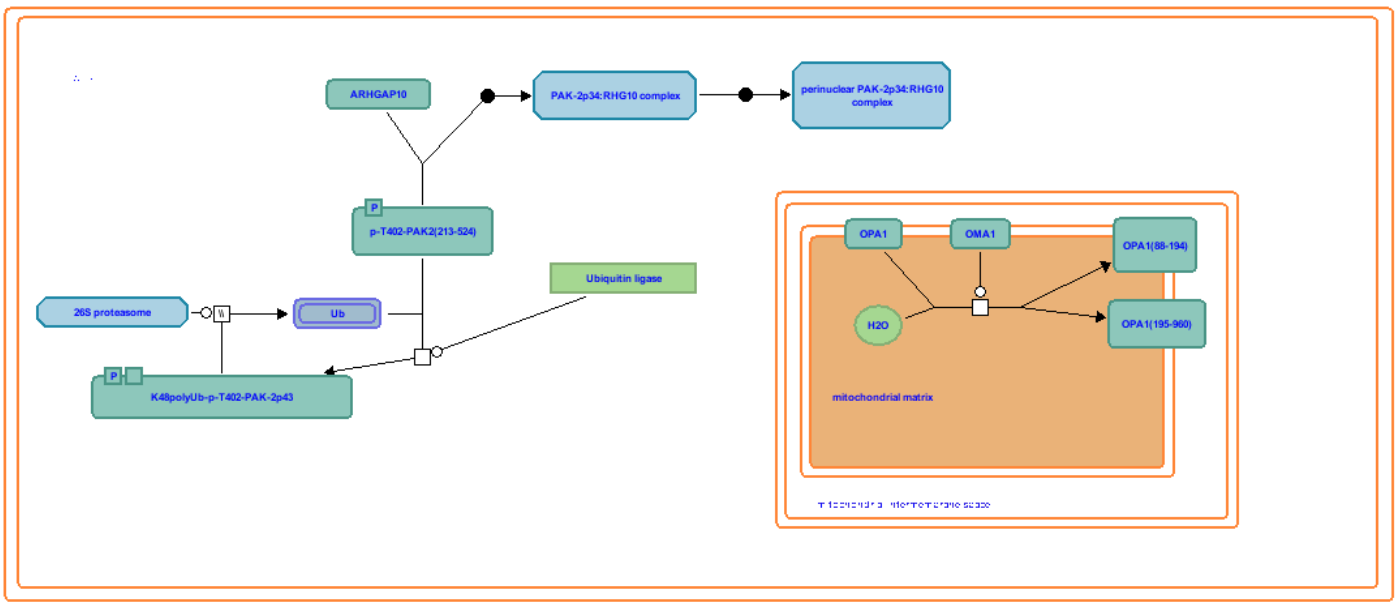
Burke D,Wilkes D,Blundell TL,Malcolm S, "Fibroblast growth factor receptors: lessons from the genes", Trends Biochem Sci, 23, 1998, 59-62.

Cunningham ML,Seto ML,Ratisoontorn C,Heike CL,Hing AV, "Syndromic craniosynostosis: from history to hydrogen bonds", Orthod Craniofac Res, 10, 2007, 67-81.

Wesche J,Haglund K,Haugsten EM, "Fibroblast growth factors and their receptors in cancer", Biochem J, 437, 2011, 199-213.

Greulich H,Pollock PM, "Targeting mutant fibroblast growth factor receptors in cancer", Trends Mol Med, 17, 2011, 283-92.

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



Summation

species name:Homo sapiens,disease name:cancer,The FGFR2 gene has been shown to be subject to activating mutations and gene amplification leading to a variety of proliferative and developmental disorders depending on whether these events occur in the germline or arise somatically. Activating FGFR2 mutations in the germline give rise to a range of craniosynostotic conditions including Pfeiffer, Apert, Jackson-Weiss, Crouzon and Beare-Stevensen Cutis Gyrata syndromes. These autosomal dominant skeletal disorders are characterized by premature fusion of several sutures in the skull, and in some cases also involve syndactyly (abnormal bone fusions in the hands and feet) (reviewed in Webster and Donoghue, 1997; Burke, 1998; Cunningham, 2007). Activating FGFR2 mutations arising somatically have been linked to the development of gastric and endometrial cancers (reviewed in Greulich and Pollock, 2011; Wesche, 2011). Many of these mutations are similar or identical to those that contribute to the autosomal disorders described above. Notably, loss-of-function mutations in FGFR2 have also been recently described in melanoma (Gartside, 2009). FGFR2 may also contribute to tumorigenesis through overexpression, as FGFR2 has been identified as a target of gene amplification in gastric and breast cancers (Kunii, 2008; Takeda, 2007).

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

Rothfels Karen,014-11-20

Editors

Rothfels Karen,014-12-05

Reviewers

Rothfels Karen,015-05-08

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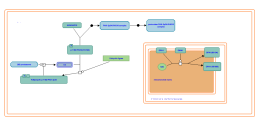
Cunningham ML,Seto ML,Ratisoontorn C,Heike CL,Hing AV, "Syndromic craniosynostosis: from history to hydrogen bonds", Orthod Craniofac Res, 10, 2007, 67-81.

Greulich H,Pollock PM, "Targeting mutant fibroblast growth factor receptors in cancer", Trends Mol Med, 17, 2011, 283-92.

Wesche J,Haglund K,Haugsten EM, "Fibroblast growth factors and their receptors in cancer", Biochem J, 437, 2011, 199-213.

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



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

P01111	P21802	Q06124	P01116	P42336	P27986
P06213	P35568	P11362			

Authors

Rothfels Karen,017-05-24

Editors

Rothfels Karen,017-05-24

Reviewers

Schmidt Esther,017-11-18

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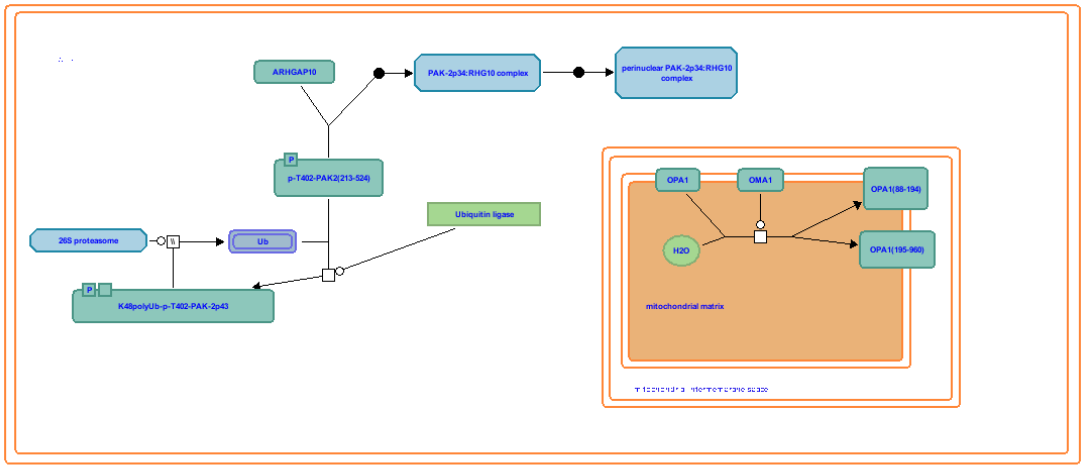
Kang DS,Yang YR,Lee C,Kim S,Ryu SH,Suh PG, "Roles of phosphoinositide-specific phospholipase C1 in brain development", Adv Biol Regul, 60, 2016, 167-73.

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

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



Summation

species name:Homo sapiens,Hemostasis is a physiological response that culminates in the arrest of bleeding from an injured vessel. Under normal conditions the vascular endothelium supports vasodilation, inhibits platelet adhesion and activation, suppresses coagulation, enhances fibrin cleavage and is anti-inflammatory in character. Under acute vascular trauma, vasoconstrictor mechanisms predominate and the endothelium becomes prothrombotic, procoagulatory and proinflammatory in nature. This is achieved by a reduction of endothelial dilating agents: adenosine, NO and prostacyclin; and by the direct action of ADP, serotonin and thromboxane on vascular smooth muscle cells to elicit their contraction (Becker et al. 2000).

The chief trigger for the change in endothelial function that leads to the formation of a haemostatic thrombus is the loss of the endothelial cell barrier between blood and extracellular matrix components (Ruggeri 2002). Circulating platelets identify and discriminate areas of endothelial lesions; here, they adhere to the exposed sub endothelium. Their interaction with the various thrombogenic substrates and locally generated or released agonists results in platelet activation. This process is described as possessing two stages, firstly, adhesion - the initial tethering to a surface, and secondly aggregation - the platelet-platelet cohesion (Savage & Cattaneo et al. 2001).

Three mechansism contribute to the loss of blood following vessel injury. The vessel constricts, reducing the loss of blood. Platelets adhere to the site of injury, become activated and aggregate with fibrinogen into a soft plug that limits blood loss, a process termed primary hemostasis. Proteins and small molecules are released from granules by activated platelets, stimulating the plug formation process. Fibrinogen from plasma forms bridges between activated platelets. These events initiate the clotting cascade (secondary hemostasis). Negatively-charged phospholipids exposed at the site of injury and on activated platelets interact with tissue factor, leading to a cascade of reactions that culminates with the formation of an insoluble fibrin clot.

List of identifiers was found at this pathway

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

Authors

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Editors

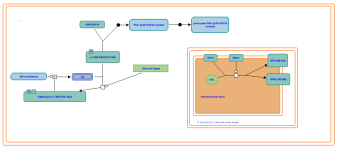
Joshi-Tope Geeta,017-11-16

Reviewers

Schmidt Esther,017-11-18

References

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



Summation

species name:Homo sapiens,The 22 members of the fibroblast growth factor (FGF) family of growth factors mediate their cellular responses by binding to and activating the different isoforms encoded by the four receptor tyrosine kinases (RTKs) designated FGFR1, FGFR2, FGFR3 and FGFR4. These receptors are key regulators of several developmental processes in which cell fate and differentiation to various tissue lineages are determined. Unlike other growth factors, FGFs act in concert with heparin or heparan sulfate proteoglycan (HSPG) to activate FGFRs and to induce the pleiotropic responses that lead to the variety of cellular responses induced by this large family of growth factors. An alternative, FGF-independent, source of FGFR activation originates from the interaction with cell adhesion molecules, typically in the context of interactions on neural cell membranes and is crucial for neuronal survival and development.Upon ligand binding, receptor dimers are formed and their intrinsic tyrosine kinase is activated causing phosphorylation of multiple tyrosine residues on the receptors. These then serve as docking sites for the recruitment of SH2 (src homology-2) or PTB (phosphotyrosine binding) domains of adaptors, docking proteins or signaling enzymes. Signaling complexes are assembled and recruited to the active receptors resulting in a cascade of phosphorylation events.This leads to stimulation of intracellular signaling pathways that control cell proliferation, cell differentiation, cell migration, cell survival and cell shape, depending on the cell type or stage of maturation.

List of identifiers was found at this pathway

P01111	P21802	Q06124	P01116	P42336	P27986
P06213	P35568	P11362	P36543		

Authors

de Bono Bernard,007-01-10

Editors

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Reviewers

Schmidt Esther,017-11-18

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Dailey L,Ambrosetti D,Mansukhani A,Basilico C, "Mechanisms underlying differential responses to FGF signaling", Cytokine Growth Factor Rev, 16, 2005, 233-47.

Zhang X,Ibrahimi OA,Olsen SK,Umemori H,Mohammadi M,Ornitz DM, "Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family.", J Biol Chem, 281, 2006, 15694-700.

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

Summation

species name:Homo sapiens,compartment name:cytosol,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.

List of identifiers was found at this pathway

P01111 P21802 Q06124 P01116 P42336 P27986
P35568 P11362

Authors

May Bruce,012-08-07

Editors

May Bruce,012-08-07

Reviewers

Schmidt Esther,017-11-18

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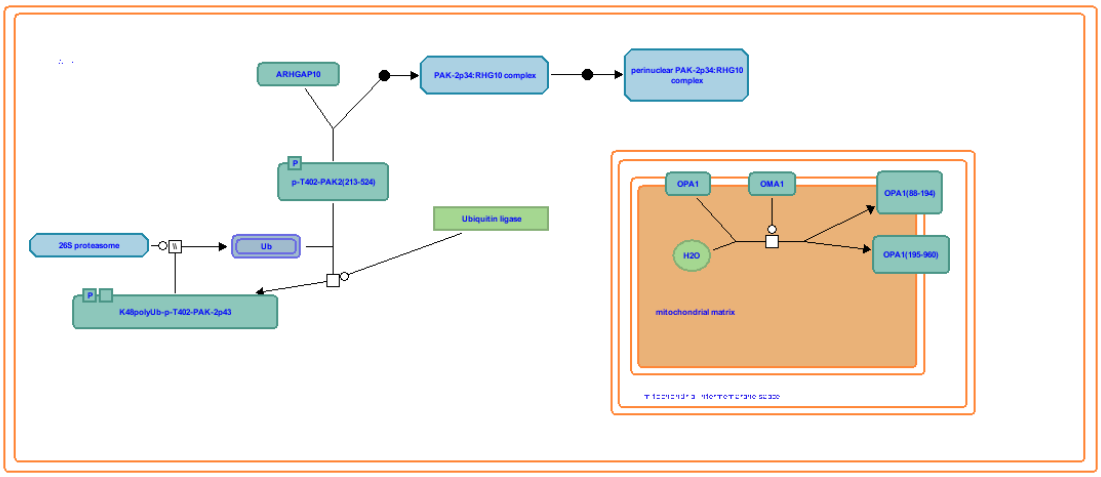
Parrella E,Longo VD, "Insulin/IGF-I and related signaling pathways regulate aging in nondividing cells: from yeast to the mammalian brain", ScientificWorldJournal, 10, 2010, 161-77.

Siddle K, "Molecular basis of signaling specificity of insulin and IGF receptors: neglected corners and recent advances", Front Endocrinol (Lausanne), 3, 2012, 34.

Maki RG, "Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer", J. Clin. Oncol., 28, 2010, 4985-95.

Annunziata M,Granata R,Ghigo E, "The IGF system", Acta Diabetol, 48, 2011, 1-9.

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



Summation

species name:Homo sapiens,compartment name:plasma membrane,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	P09619	P04626	P21802	P10721	P01116
P21860	P46940	P35568	Q06124	Q7Z5R6	Q14738
P16234	P11362	P05106	P02751	P00533	P08581

Authors

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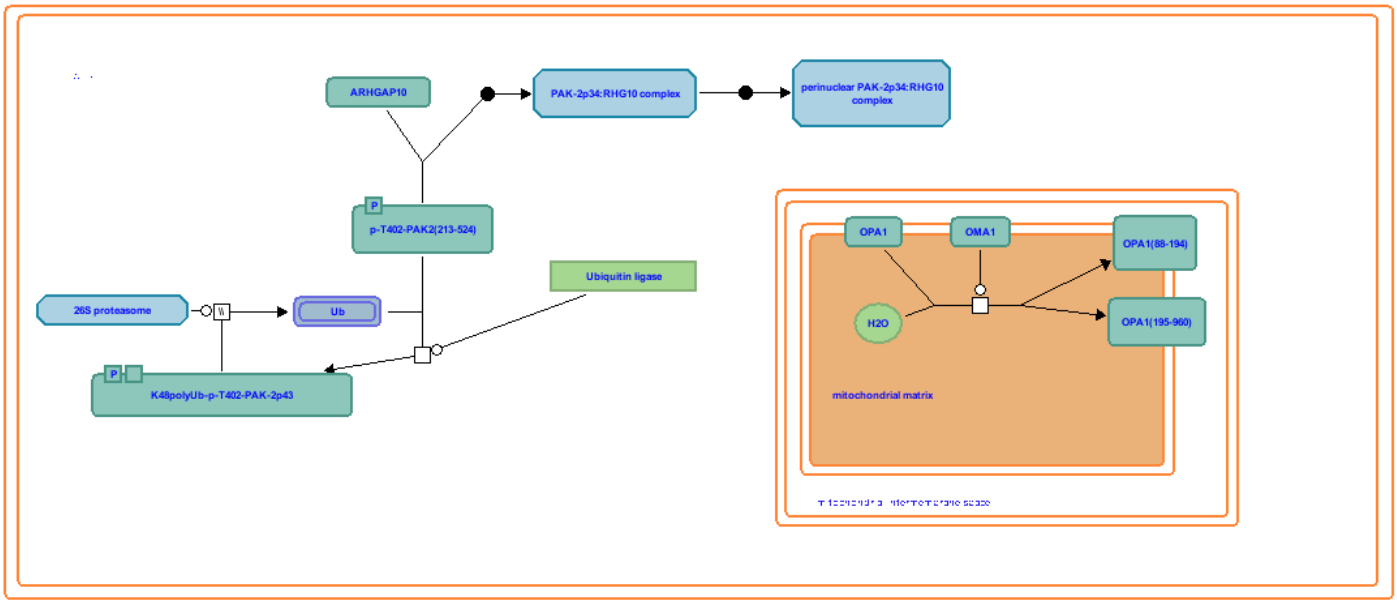
Reviewers

Schmidt Esther,017-11-18

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



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.

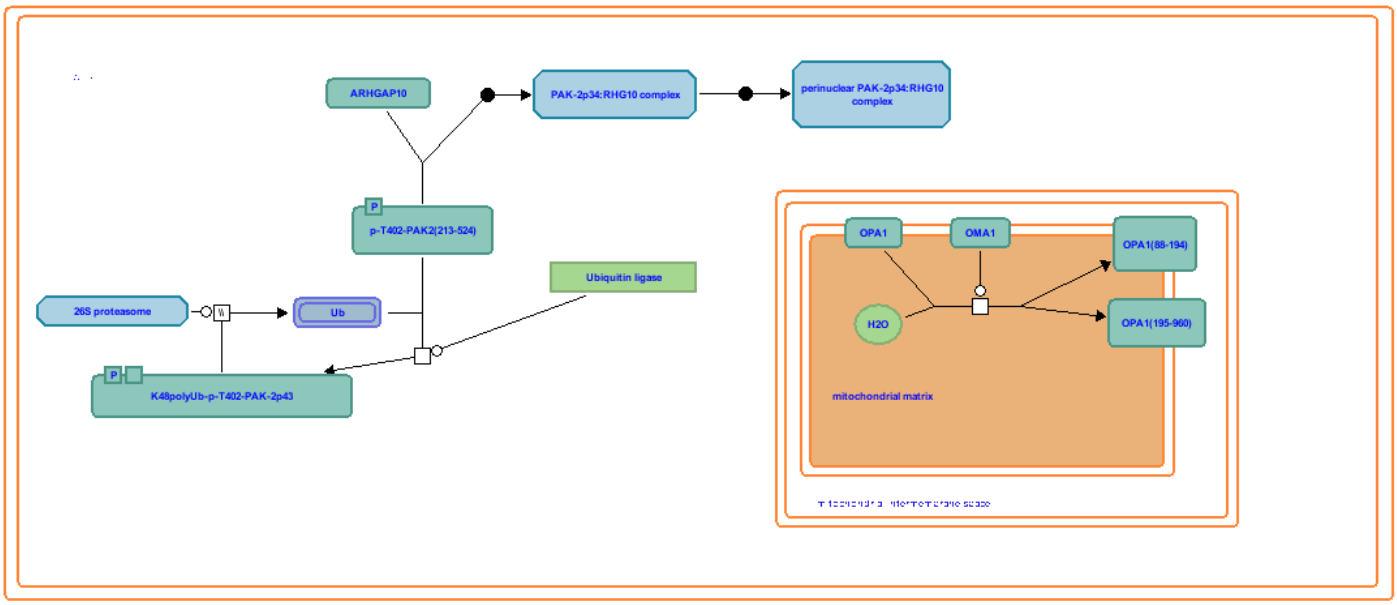
List of identifiers was found at this pathway

P01111	P09619	P56945	Q06124	P01116	P40763
P42336	P27986	P42224	P16234		

Reviewers

Schmidt Esther,017-11-18

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



Summation

species name:Homo sapiens,disease name:cancer,In glioblastoma, the most prevalent EGFR mutation, present in ~25% of tumors, is the deletion of the ligand binding domain of EGFR, accompanied with amplification of the mutated allele, which results in over-expression of the mutant protein known as EGFRvIII. EGFRvIII mutant is not able to bind a ligand, but dimerizes and autophosphorylates spontaneously and is therefore constitutively active (Fernandes et al. 2001). Point mutations in the extracellular domain of EGFR are also frequently found in glioblastoma, but ligand binding ability and responsiveness are preserved (Lee et al. 2006). Similar to EGFR kinase domain mutants, EGFRvIII mutant needs to maintain association with the chaperone heat shock protein 90 (HSP90) for proper functioning (Shimamura et al. 2005, Lavictoire et al. 2003). CDC37 is a co-chaperone of HSP90 that acts as a scaffold and regulator of interaction between HSP90 and its protein kinase clients. CDC37 is frequently over-expressed in cancers involving mutant kinases and acts as an oncogene (Roe et al. 2004, reviewed by Gray Jr. et al. 2008). Expression of EGFRvIII mutant results in aberrant activation of downstream signaling cascades, namely RAS/RAF/MAP kinase signaling and PI3K/AKT signaling, and possibly signaling by PLCG1, which leads to increased cell proliferation and survival, providing selective advantage to cancer cells that harbor EGFRvIII (Huang et al. 2007). EGFRvIII mutant does not autophosorylate on the tyrosine residue Y1045, a docking site for CBL, and is therefore unable to recruit CBL ubiquitin ligase, which enables it to escape degradation (Han et al. 2006)

List of identifiers was found at this pathway

P01111 P21802 Q06124 P01116 P42336 P27986
P35568 P11362

Authors

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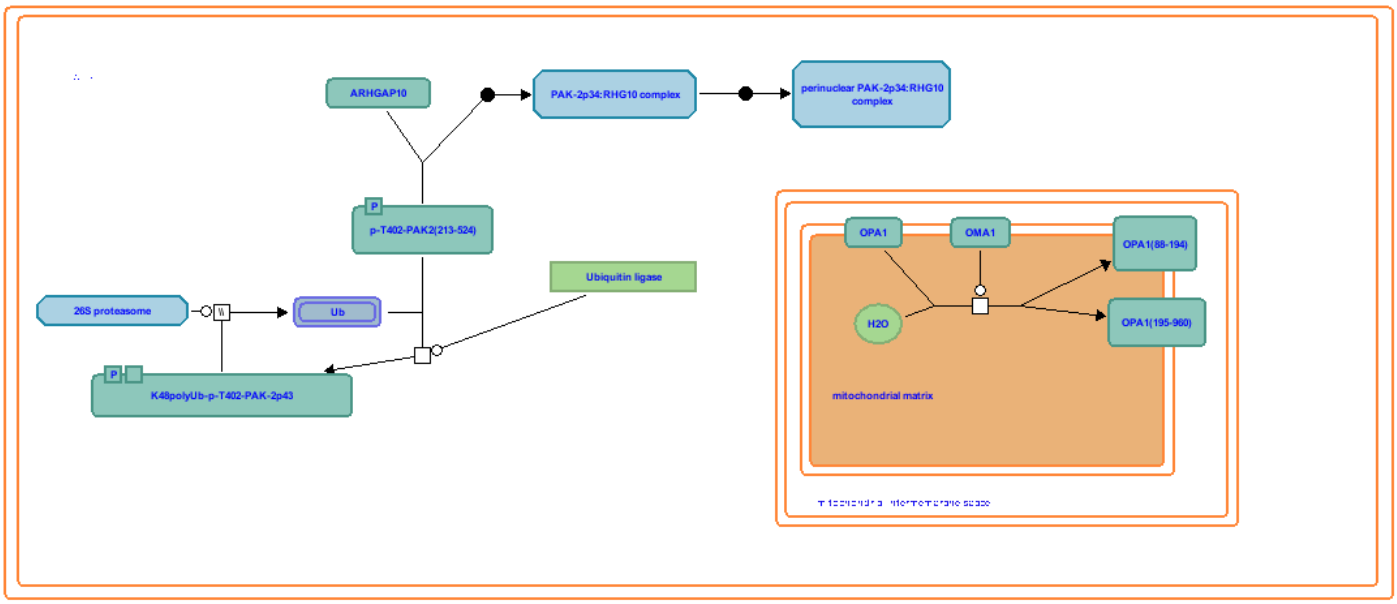
2.22. Signaling by FGFR1 in disease (R-HSA-5655302)



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

P01111 P01116 O15164 P40763 P42336 P27986
P42224 P11274 P11362

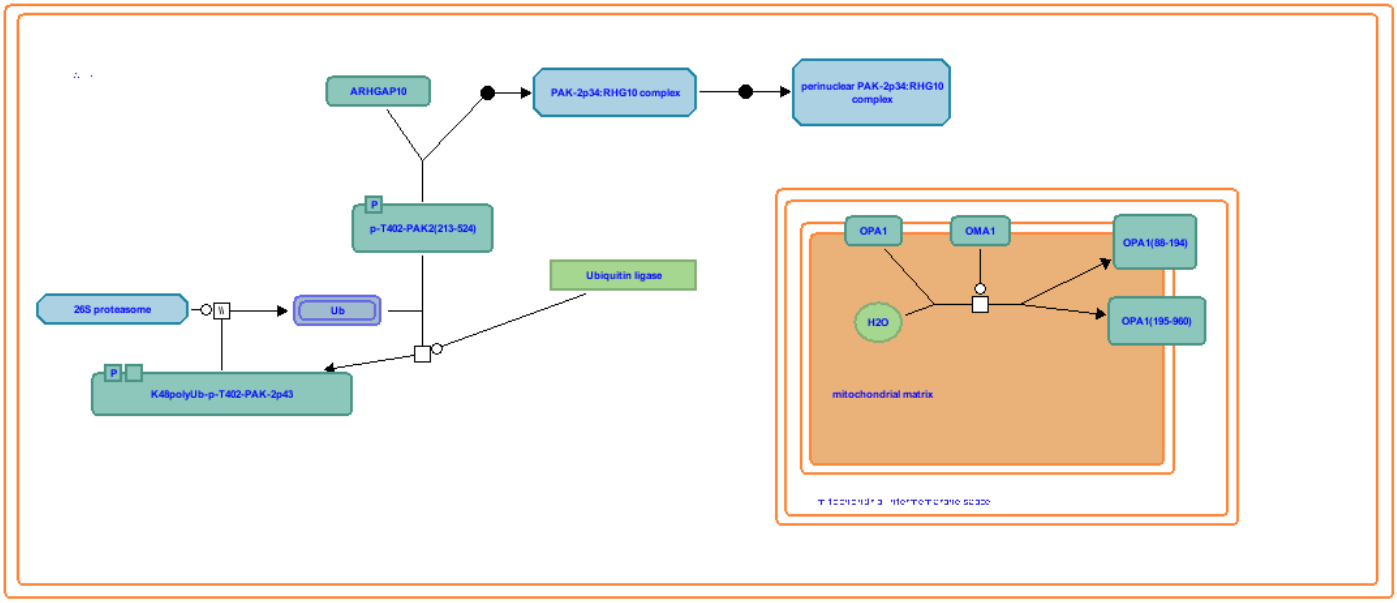
Authors

Nasi null,006-10-10Annibali null,006-10-10

Reviewers

Croft David,017-12-04

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



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	P21802	Q06124	P01116	P42336	P27986
P35568	P11362				

Authors

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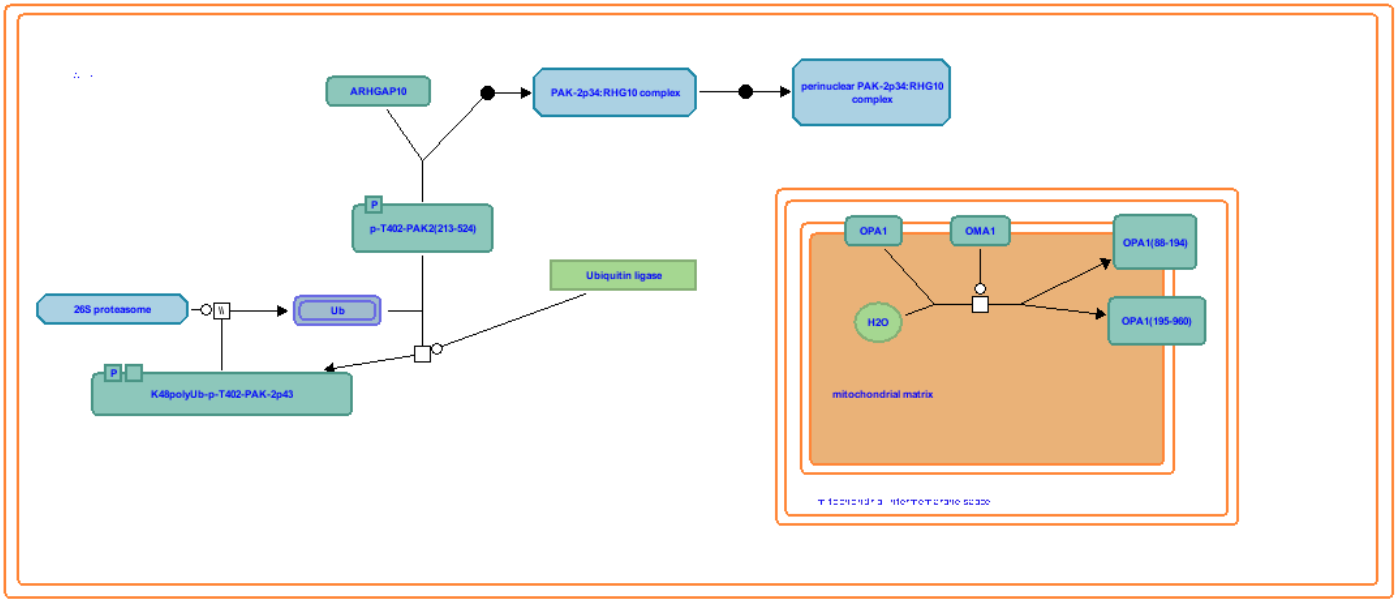
receptors", Biochim Biophys Acta, 1378, 1998, F79-113.

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



Summation

species name:Homo sapiens,MET is a receptor tyrosine kinase (RTK) (Cooper et al. 1984, Park et al. 1984) activated by binding to its ligand, Hepatocyte growth factor/Scatter factor (HGF/SF) (Bottaro et al. 1991, Naldini et al. 1991). Similar to other related RTKs, such as EGFR, ligand binding induces MET dimerization and trans-autophosphorylation, resulting in the active MET receptor complex (Ferracini et al. 1991, Longati et al. 1994, Rodrigues and Park 1994, Kirchhofer et al. 2004, Stamos et al. 2004, Hays and Watowich 2004). Phosphorylated tyrosines in the cytoplasmic tail of MET serve as docking sites for binding of adapter proteins, such as GRB2, SHC1 and GAB1, which trigger signal transduction cascades that activate PI3K/AKT, RAS, STAT3, PTK2, RAC1 and RAP1 signaling (Ponzetto et al. 1994, Pelicci et al. 1995, Weidner et al. 1995, Besser et al. 1997, Shen and Novak 1997, Beviglia and Kramer 1999, Rodrigues et al. 2000, Sakkab et al. 2000, Schaeper et al. 2000, Lamorte et al. 2002, Wang et al. 2002, Chen and Chen 2006, Palamidessi et al. 2008, Chen et al. 2011, Murray et al. 2014).Activation of PLC gamma 1 (PLCG1) signaling by MET remains unclear. It has been reported that PLCG1 can bind to MET directly (Ponzetto et al. 1994) or be recruited by phosphorylated GAB1 (Gual et al. 2000). Tyrosine residue Y307 of GAB1 that serves as docking sites for PLCG1 may be phosphorylated either by activated MET (Watanabe et al. 2006) or SRC (Chan et al. 2010). Another PCLG1 docking site on GAB1, tyrosine residue Y373, was reported as the SRC target, while the kinase for the main PLCG1 docking site, Y407 of GAB1, is not known (Chan et al. 2010).Signaling by MET promotes cell growth, cell survival and motility, which are essential for embryonic development (Weidner et al. 1993, Schmidt et al. 1995, Uehara et al. 1995, Bladt et al. 1995, Maina et al. 1997, Maina et al. 2001, Helmbacher et al. 2003) and tissue regeneration (Huh et al. 2004, Borowiak et al. 2004, Liu 2004, Chmielowiec et al. 2007). MET signaling is frequently aberrantly activated in cancer, through MET overexpression or activating MET mutations (Schmidt et al. 1997, Pennacchietti et al. 2003, Smolen et al. 2006, Bertotti et al. 2009).Considerable progress has recently been made in the development of HGF-MET inhibitors in cancer therapy. These include inhibitors of HGF activators, HGF inhibitors and MET antagonists, which are protein therapeutics that act outside the cell. Kinase inhibitors function inside the cell and have constituted the largest effort towards MET-based therapeutics (Gherardi et al. 2012).Pathogenic bacteria of the species Listeria monocytogenes, exploit MET receptor as an entryway to host cells (Shen et al. 2000, Veiga and Cossart 2005, Neimann et al. 2007).For review of MET signaling,

please refer to Birchmeier et al. 2003, Trusolino et al. 2010, Gherardi et al. 2012, Petrini 2015.

List of identifiers was found at this pathway

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

Authors

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Orlic-Milacic Marija,016-06-14

Reviewers

Schmidt Esther,017-11-18

References

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Gual P,Giordano S,Williams TA,Rocchi S,Van Obberghen E,Comoglio PM, "Sustained recruitment of phospholipase C-gamma to Gab1 is required for HGF-induced branching tubulogenesis", Oncogene, 19, 2000, 1509-18.

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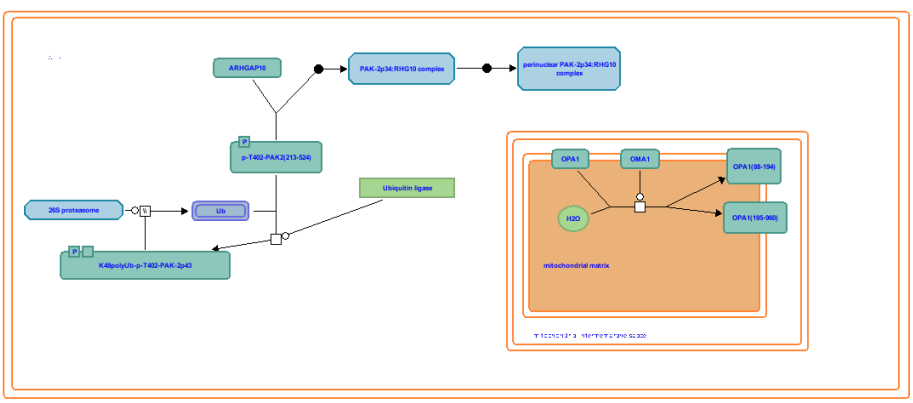
2.25. Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R) (R-HSA-2404192)



Summation

species name:Homo sapiens,The mitogen activated protein kinases (MAPKs) are a family of conserved protein serine threonine kinases that respond to varied extracellular stimuli to activate intracellular processes including gene expression, metabolism, proliferation, differentiation and apoptosis, among others. The classic MAPK cascades, including the ERK1/2 pathway, the p38 MAPK pathway, the JNK pathway and the ERK5 pathway are characterized by three tiers of sequentially acting, activating kinases (reviewed in Kryiakis and Avruch, 2012; Cargnello and Roux, 2011). The MAPK kinase kinase kinase (MAPKKK), at the top of the cascade, is phosphorylated on serine and threonine residues in response to external stimuli; this phosphorylation often occurs in the context of an interaction between the MAPKKK protein and a member of the RAS/RHO family of small GTP-binding proteins. Activated MAPKKK proteins in turn phosphorylate the dual-specificity MAPK kinase proteins (MAPKK), which ultimately phosphorylate the MAPK proteins in a conserved Thr-X-Tyr motif in the activation loop. Less is known about the activation of the atypical families of MAPKs, which include the ERK3/4 signaling cascade, the ERK7 cascade and the NLK cascade. Although the details are not fully worked out, these MAPK proteins don't appear to be phosphorylated downstream of a 3-tiered kinase system as described above (reviewed in Coulombe and Meloche, 2007; Cargnello and Roux, 2011) . Both conventional and atypical MAPKs are proline-directed serine threonine kinases and, once activated, phosphorylate substrates in the consensus P-X-S/T-P site. Both cytosolic and nuclear targets of MAPK proteins have been identified and upon stimulation, a proportion of the phosphorylated MAPKs relocalize from the cytoplasm to the nucleus. In some cases, nuclear translocation may be accompanied by dimerization, although the relationship between these two events is not fully elaborated (reviewed in Kryiakis and Avruch, 2012; Cargnello and Roux, 2011; Plotnikov et al, 2010).

List of identifiers was found at this pathway

P01111	P21802	Q06124	P01116	P42336	P27986
P35568	P11362				

Authors

Rothfels Karen,015-03-10

Reviewers

Schmidt Esther,017-11-18

References

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

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

2.26. MAPK family signaling cascades (R-HSA-5683057)

Summation

species name:Homo sapiens,Interleukin-4 (IL4) is a principal regulatory cytokine during the immune response, crucially important in allergy and asthma (Nelms et al. 1999). When resting T cells are antigen-activated and expand in response to Interleukin-2 (IL2), they can differentiate as Type 1 (Th1) or Type 2 (Th2) T helper cells. The outcome is influenced by IL4. Th2 cells secrete IL4, which both stimulates Th2 in an autocrine fashion and acts as a potent B cell growth factor to promote humoral immunity (Nelms et al. 1999). Interleukin-13 (IL13) is an immunoregulatory cytokine secreted predominantly by activated Th2 cells. It is a key mediator in the pathogenesis of allergic inflammation. IL13 shares many functional properties with IL4, stemming from the fact that they share a common receptor subunit. IL13 receptors are expressed on human B cells, basophils, eosinophils, mast cells, endothelial cells, fibroblasts, monocytes, macrophages, respiratory epithelial cells, and smooth muscle cells, but unlike IL4, not T cells. Thus IL13 does not appear to be important in the initial differentiation of CD4 T cells into Th2 cells, rather it is important in the effector phase of allergic inflammation (Hershey et al. 2003).

IL4 and IL13 induce “alternative activation” of macrophages, inducing an anti-inflammatory phenotype by signaling through IL4R alpha in a STAT6 dependent manner. This signaling plays an important role in the Th2 response, mediating anti-parasitic effects and aiding wound healing (Gordon & Martinez 2010, Loke et al. 2002)

There are two types of IL4 receptor complex (Andrews et al. 2006). Type I IL4R (IL4R1) is predominantly expressed on the surface of hematopoietic cells and consists of IL4R and IL2RG, the common gamma chain. Type II IL4R (IL4R2) is predominantly expressed on the surface of nonhematopoietic cells, it consists of IL4R and IL13RA1 and is also the type II receptor for IL13. (Obiri et al. 1995, Aman et al. 1996, Hilton et al. 1996, Miloux et al. 1997, Zhang et al. 1997). The second receptor for IL13 consists of IL4R and Interleukin-13 receptor alpha 2 (IL13RA2), sometimes called Interleukin-13 binding protein (IL13BP). It has a high affinity receptor for IL13 (Kd = 250 pmol/L) but is not sufficient to render cells responsive to IL13, even in the presence of IL4R (Donaldson et al. 1998). It is reported to exist in soluble form (Zhang et al. 1997) and when overexpressed reduces JAK-STAT signaling (Kawakami et al. 2001). It's function may be to prevent IL13 signalling via the functional IL4R:IL13RA1 receptor. IL13RA2 is overexpressed and enhances cell invasion in some human cancers (Joshi & Puri 2012).The first step in the formation of IL4R1 (IL4:IL4R:IL2RB) is the binding of IL4 with IL4R (Hoffman et al. 1995, Shen et al. 1996, Hage et al. 1999). This is also the first step in formation of IL4R2 (IL4:IL4R:IL13RA1). After the initial binding of IL4 and IL4R, IL2RB binds (LaPorte et al. 2008), to form IL4R1. Alternatively, IL13RA1 binds, forming IL4R2. In contrast, the type II IL13 complex (IL13R2) forms with IL13 first binding to IL13RA1 followed by recruitment of IL4R (Wang et al. 2009).Crystal structures of the IL4:IL4R:IL2RG, IL4:IL4R:IL13RA1 and IL13:IL4R:IL13RA1 complexes have been determined (LaPorte et al. 2008). Consistent with these structures, in monocytes IL4R is tyrosine phosphorylated in response to both IL4 and IL13 (Roy et al. 2002, Gordon & Martinez 2010) while IL13RA1 phosphorylation is induced only by IL13 (Roy et al. 2002, LaPorte et al. 2008) and IL2RG phosphorylation is induced only by IL4 (Roy et al. 2002).Both IL4 receptor complexes signal through Jak/STAT cascades. IL4R is constitutively-associated with JAK2 (Roy et al. 2002) and associates with JAK1 following binding of IL4 (Yin et al. 1994) or IL13 (Roy et al. 2002). IL2RG constitutively associates with JAK3 (Boussiotis et al. 1994, Russell et al. 1994). IL13RA1 constitutively associates with TYK2 (Umeshita-Suyama et al. 2000, Roy et al. 2002, LaPorte et al. 2008, Bhattacharjee et al. 2013). IL4 binding to IL4R1 leads to phosphorylation of JAK1 (but not JAK2) and STAT6 activation (Takeda et al. 1994, Ratthe et al. 2007, Bhattacharjee et al. 2013). IL13 binding increases activating tyrosine-99 phosphorylation of IL13RA1 but not that of IL2RG. IL4 binding to IL2RG leads to its tyrosine phosphorylation (Roy et al. 2002). IL13 binding to IL4R2 leads to TYK2 and JAK2 (but not JAK1) phosphorylation (Roy & Cathcart 1998, Roy et al. 2002).Phosphorylated TYK2 binds and phosphorylates STAT6 and possibly STAT1 (Bhattacharjee et al. 2013). A second mechanism of signal

transduction activated by IL4 and IL13 leads to the insulin receptor substrate (IRS) family (Kelly-Welch et al. 2003). IL4R1 associates with insulin receptor substrate 2 and activates the PI3K/Akt and Ras/MEK/Erk pathways involved in cell proliferation, survival and translational control. IL4R2 does not associate with insulin receptor substrate 2 and consequently the PI3K/Akt and Ras/MEK/Erk pathways are not activated (Busch-Dienstfertig & González-Rodríguez 2013).

List of identifiers was found at this pathway

P01111	P09619	P04626	P21802	P10721	P01116
P21860	P46940	P35568	Q06124	Q7Z5R6	Q14738
P16234	P11362	O43524	P05106	P02751	P00533
P08581					

Authors

Jupe Steve,015-07-01

Editors

Jupe Steve,016-09-02

Reviewers

Croft David,017-12-04

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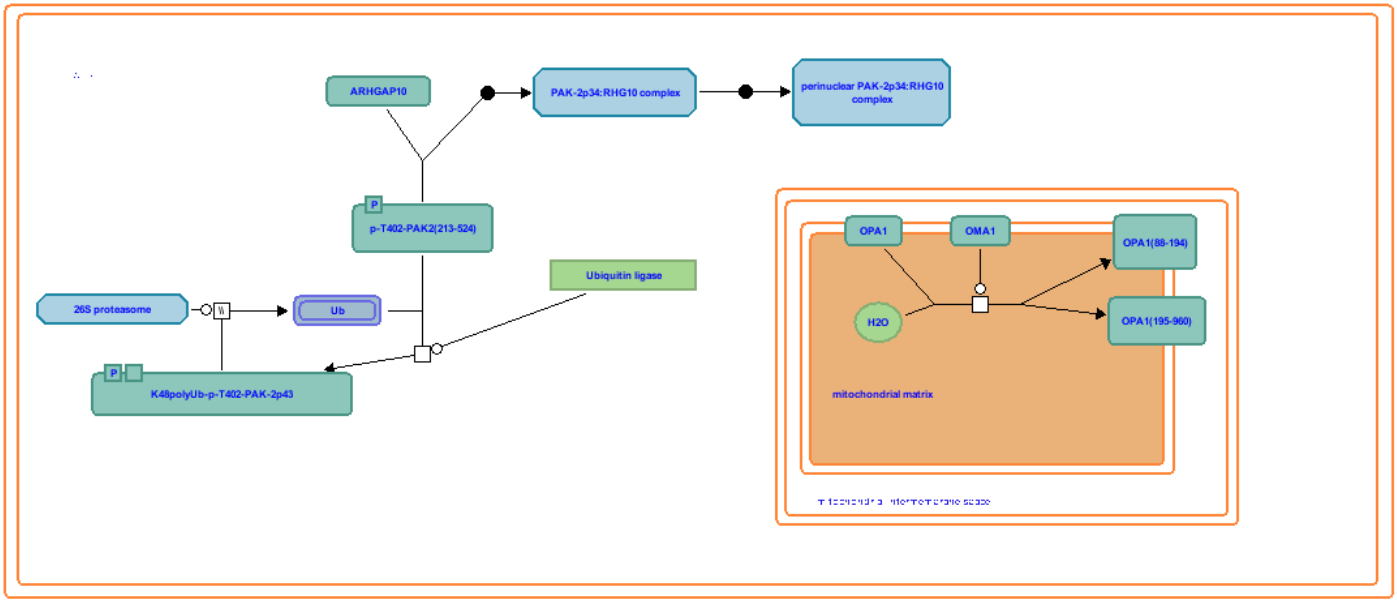
2.27. Platelet activation, signaling and aggregation (R-HSA-76002)



Summation

species name:Homo sapiens,compartment name:plasma membrane,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).

List of identifiers was found at this pathway

P01011	O15439	P56945	P08123	P27986	P05771
Q05513	P49619	Q05655	P63096	Q06124	P07948
P17252	Q7Z5R6	P01023	P02452	P05106	P02751
Q16760	P42336	P09486	P52735		

Authors

May Bruce,012-07-08

Editors

May Bruce,012-07-08

Reviewers

Croft David,017-12-04

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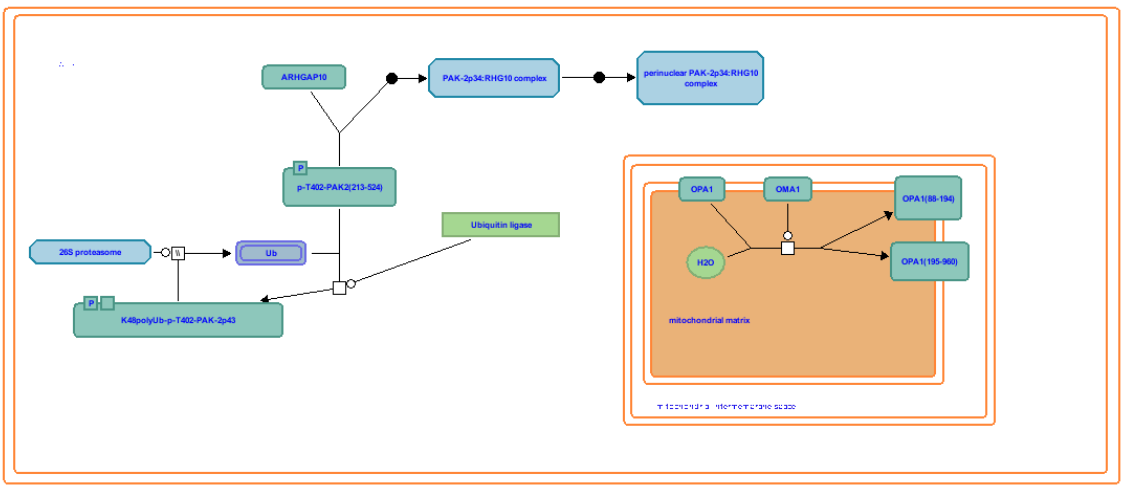
Maki RG, "Small is beautiful: insulin-like growth factors and their role in growth, development, and cancer", J. Clin. Oncol., 28, 2010, 4985-95.

Chitnis MM,Yuen JS,Protheroe AS,Pollak M,Macaulay VM, "The type 1 insulin-like growth factor receptor pathway", Clin. Cancer Res., 14, 2008, 6364-70.

Parrella E,Longo VD, "Insulin/IGF-I and related signaling pathways regulate aging in nondividing cells: from yeast to the mammalian brain", ScientificWorldJournal, 10, 2010, 161-77.

2.28. Hemostasis (R-HSA-109582)



Summation

species name:Homo sapiens,disease name:cancer,While AKT1 gene copy number, expression level and phosphorylation are often increased in cancer, only one low frequency point mutation has been repeatedly reported in cancer and functionally studied. This mutation represents a substitution of a glutamic acid residue with lysine at position 17 of AKT1, and acts by enabling AKT1 to bind PIP2. PIP2-bound AKT1 is phosphorylated by TORC2 complex and by 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).

List of identifiers was found at this pathway

P01111	P56945	P01116	P27986	P63092	O15439
Q05513	P49619	Q06124	P17252	P63096	P02452
P07948	O15066	P04637	P02751	P29474	P42336
P23771	P09486	P05771	Q09472	P01011	P04921
P08123	P30291	Q05655	Q7Z5R6	Q14738	P01023
P05106	P05107	Q16760	Q14185	P52735	

Authors

Orlic-Milacic Marija,012-07-18

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Croft David,017-12-04

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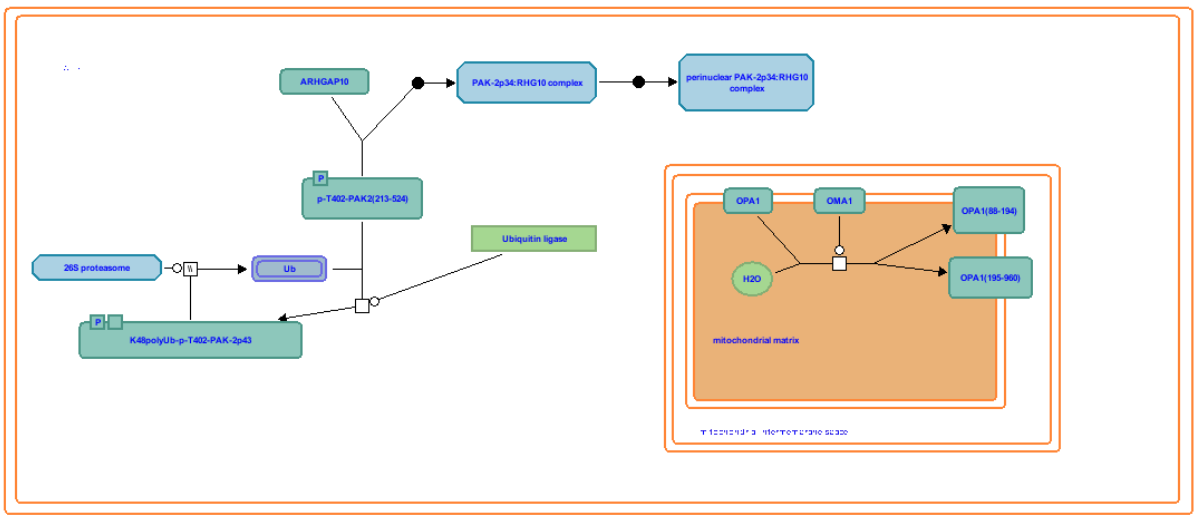
Landgraf KE,Pilling C,Falke JJ, "Molecular mechanism of an oncogenic mutation that alters membrane targeting: Glu17Lys modifies the PIP lipid specificity of the AKT1 PH domain", Biochemistry, 47, 2008, 12260-9.

2.29. Signaling by MET (R-HSA-6806834)



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

P02452	P01111	P02751	Q06124	P01116	P08123
P40763	P08581	P42336	P27986	P22681	P02461

Authors

Bevan A Paul,005-05-06Charalambous Marika,005-05-06Gopinathrao G,005-05-06Joshi-Tope Geeta,005-05-06Rothfels Karen,005-05-06Orlic-Milacic Marija,005-05-06

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Schmidt Esther,017-11-18

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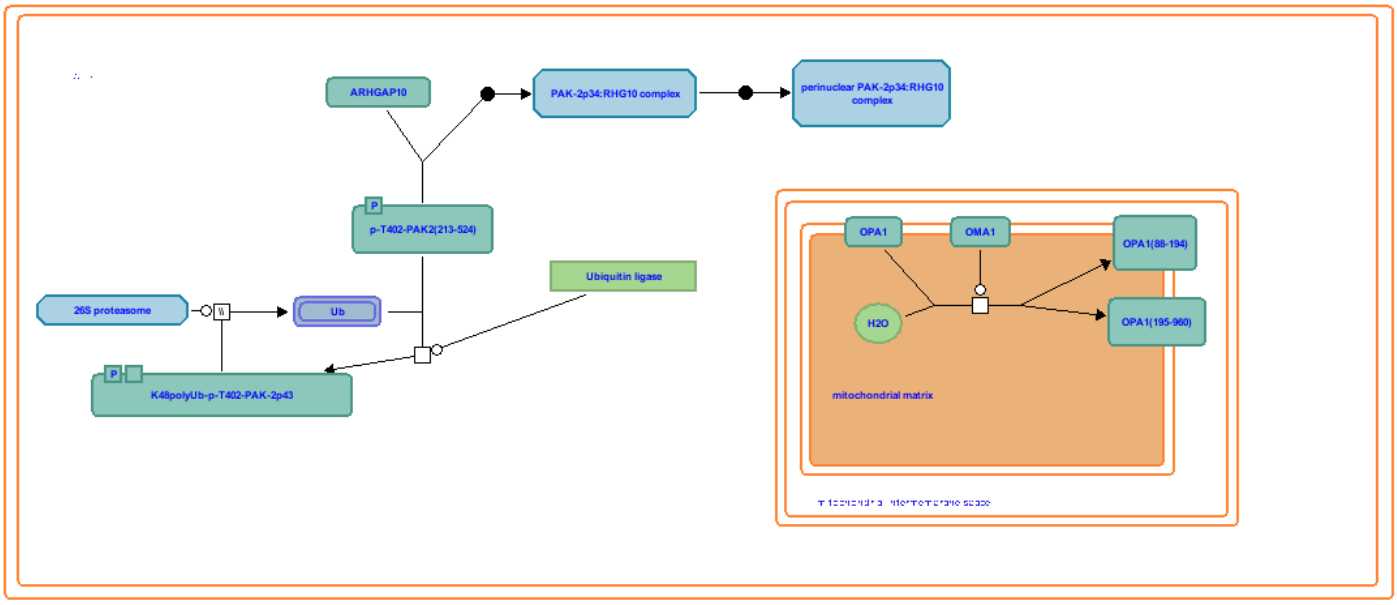
2.30. PI3K Cascade (R-HSA-109704)



Summation

species name:Homo sapiens,Axon guidance / axon pathfinding is the process by which neurons send out axons to reach the correct targets. Growing axons have a highly motile structure at the growing tip called the growth cone, which senses the guidance cues in the environment through guidance cue receptors and responds by undergoing cytoskeletal changes that determine the direction of axon growth. Guidance cues present in the surrounding environment provide the necessary directional information for the trip. These extrinsic cues have been divided into attractive or repulsive signals that tell the growth cone where and where not to grow. Genetic and biochemical studies have led to the identification of highly conserved families of guidance molecules and their receptors that guide axons. These include netrins, Slits, semaphorins, and ephrins, and their cognate receptors, DCC and or uncoordinated-5 (UNC5), roundabouts (Robo), neuropilin and Eph. In addition, many other classes of adhesion molecules are also used by growth cones to navigate properly which include NCAM and L1CAM.

List of identifiers was found at this pathway

P21802 P42336 Q06124 P35568 P27986 P11362

Authors

Garapati Phani Vijay,009-05-29

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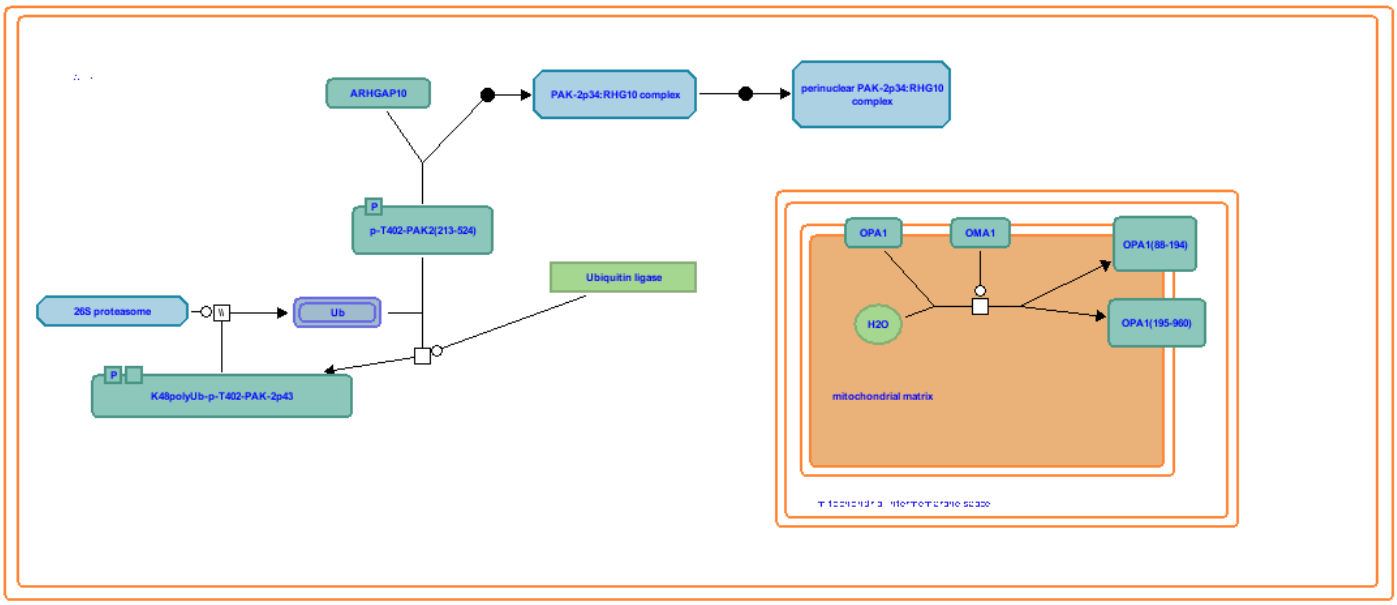
Garapati Phani Vijay,009-05-29

Reviewers

Schmidt Esther,017-11-18

2.31. Downstream signaling of activated FGFR2 (R-HSA-5654696)



Summation

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

List of identifiers was found at this pathway

P21802 P42336 P01111 Q06124 P01116 P27986

Authors

Rothfels Karen,017-05-24

Editors

Rothfels Karen,017-05-24

Reviewers

Schmidt Esther,017-11-18

References

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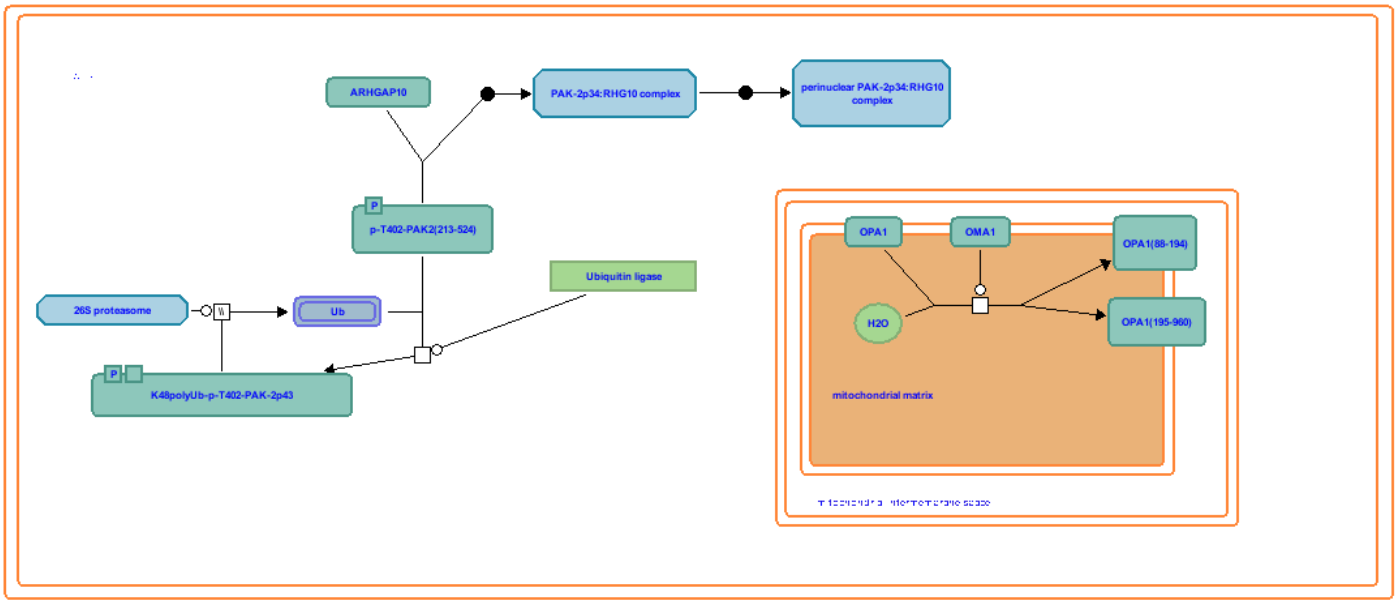
2.32. FGFR1 mutant receptor activation (R-HSA-1839124)



Summation

species name:Homo sapiens,compartment name:plasma membrane,Interleukins are low molecular weight proteins that bind to cell surface receptors and act in an autocrine and/or paracrine fashion. They were first identified as factors produced by leukocytes but are now known to be produced by many other cells throughout the body. They have pleiotropic effects on cells which bind them, impacting processes such as tissue growth and repair, hematopoietic homeostasis, and multiple levels of the host defense against pathogens where they are an essential part of the immune system.

List of identifiers was found at this pathway

O15164 P40763 P42336 P27986 P42224 P11274 P11362

Authors

Ray Keith,010-05-17

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Schmidt Esther,017-11-18

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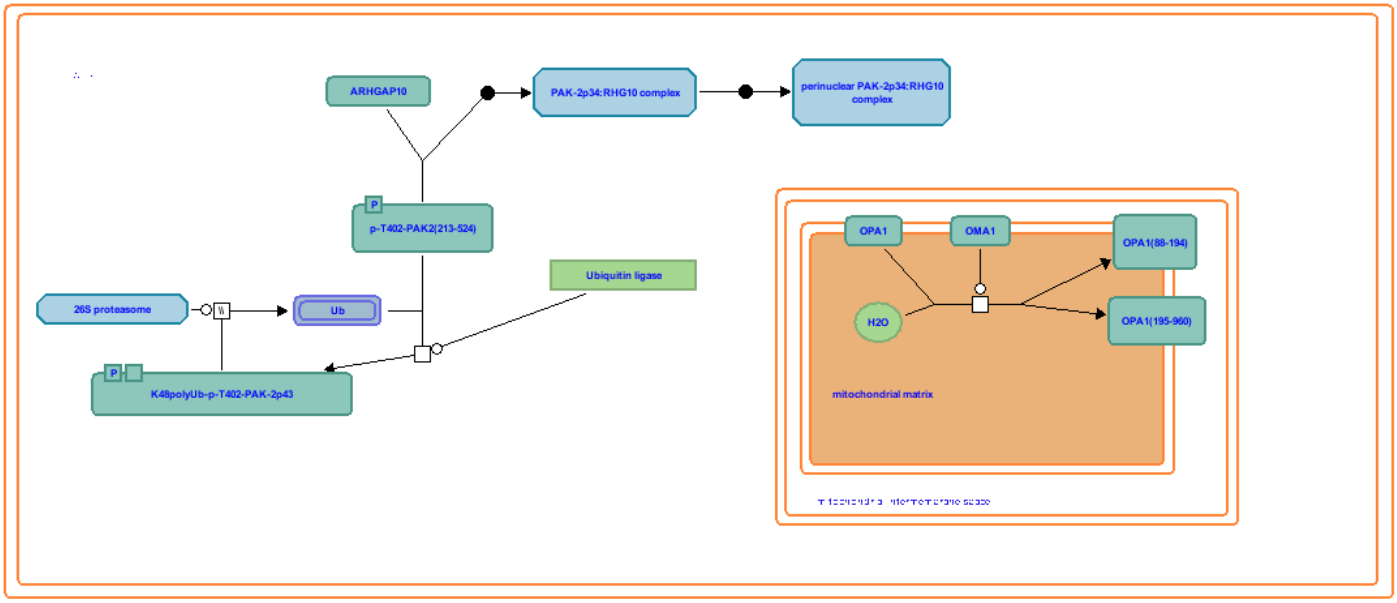
Akdis M,Aab A,Altunbulakli C,Azkur K,Costa RA,Crameri R,Duan S,Eiwegger T,Eljaszewicz A,Ferstl R,Frei R,Garbani M,Globinska A,Hess L,Huitema C,Kubo T,Komlosi Z,Konieczna P,Kovacs N,Kucuksezer UC,Meyer N,Morita H,Olzhausen J,O'Mahony L,Pezer M,Prati M,Rebane A,Rhyner C,Rinaldi A,Sokolowska M,Stanic B,Sugita K,Treis A,Van De Veen W,Wanke K,Wawrzyniak M,Wawrzyniak P,Wirz OF,Zakzuk JS,Akdis CA, "Interleukins (from IL-1 to IL-38), interferons, transforming growth factor , and TNF-: Receptors, functions, and roles in diseases", J. Allergy Clin. Immunol., 138, 2016, 984-1010.

2.33. Signaling by FGFR2 in disease (R-HSA-5655253)



Summation

species name:Homo sapiens,The 22 members of the fibroblast growth factor (FGF) family of growth factors mediate their cellular responses by binding to and activating the different isoforms encoded by the four receptor tyrosine kinases (RTKs) designated FGFR1, FGFR2, FGFR3 and FGFR4. These receptors are key regulators of several developmental processes in which cell fate and differentiation to various tissue lineages are determined. Unlike other growth factors, FGFs act in concert with heparin or heparan sulfate proteoglycan (HSPG) to activate FGFRs and to induce the pleiotropic responses that lead to the variety of cellular responses induced by this large family of growth factors. An alternative, FGF-independent, source of FGFR activation originates from the interaction with cell adhesion molecules, typically in the context of interactions on neural cell membranes and is crucial for neuronal survival and development.Upon ligand binding, receptor dimers are formed and their intrinsic tyrosine kinase is activated causing phosphorylation of multiple tyrosine residues on the receptors. These then serve as docking sites for the recruitment of SH2 (src homology-2) or PTB (phosphotyrosine binding) domains of adaptors, docking proteins or signaling enzymes. Signaling complexes are assembled and recruited to the active receptors resulting in a cascade of phosphorylation events.This leads to stimulation of intracellular signaling pathways that control cell proliferation, cell differentiation, cell migration, cell survival and cell shape, depending on the cell type or stage of maturation.

List of identifiers was found at this pathway

P21802 P42336 P01111 P01116 P27986

Authors

de Bono Bernard,007-01-10

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de Bono Bernard,007-02-11D'Eustachio Peter,007-02-11

Reviewers

Schmidt Esther,017-11-18

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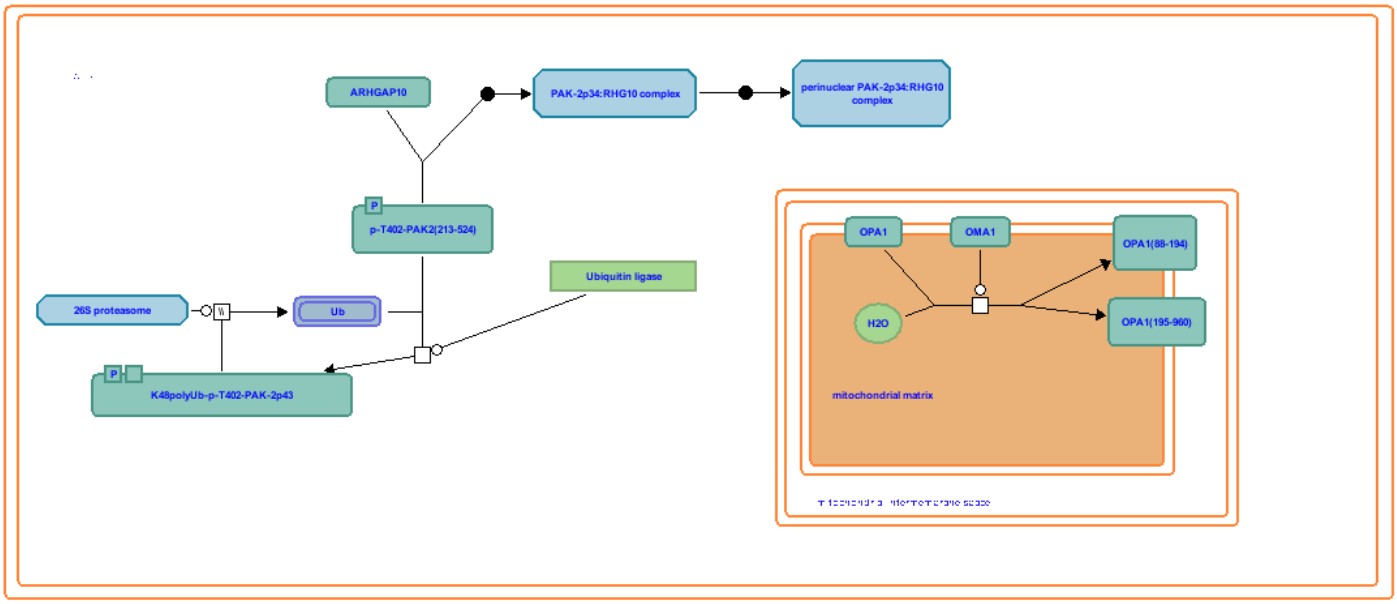
Zhang X,Ibrahimi OA,Olsen SK,Umemori H,Mohammadi M,Ornitz DM, "Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family.", J Biol Chem, 281, 2006, 15694-700.

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



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	P21802	Q06124	P01116	P42336	P27986
P22681	P11362				

Authors

Garapati Phani Vijay,013-08-30

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Schmidt Esther,017-11-18

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

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

Summation

species name:Homo sapiens,disease name: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.

List of identifiers was found at this pathway

P07900	P01111	Q05655	P17252	P04626	P00533
P01116	P21860	P42336	P27986		

Authors

Orlic-Milacic Marija,012-07-18

Editors

Matthews Lisa,012-08-03

Reviewers

Orlic-Milacic Marija,015-02-12

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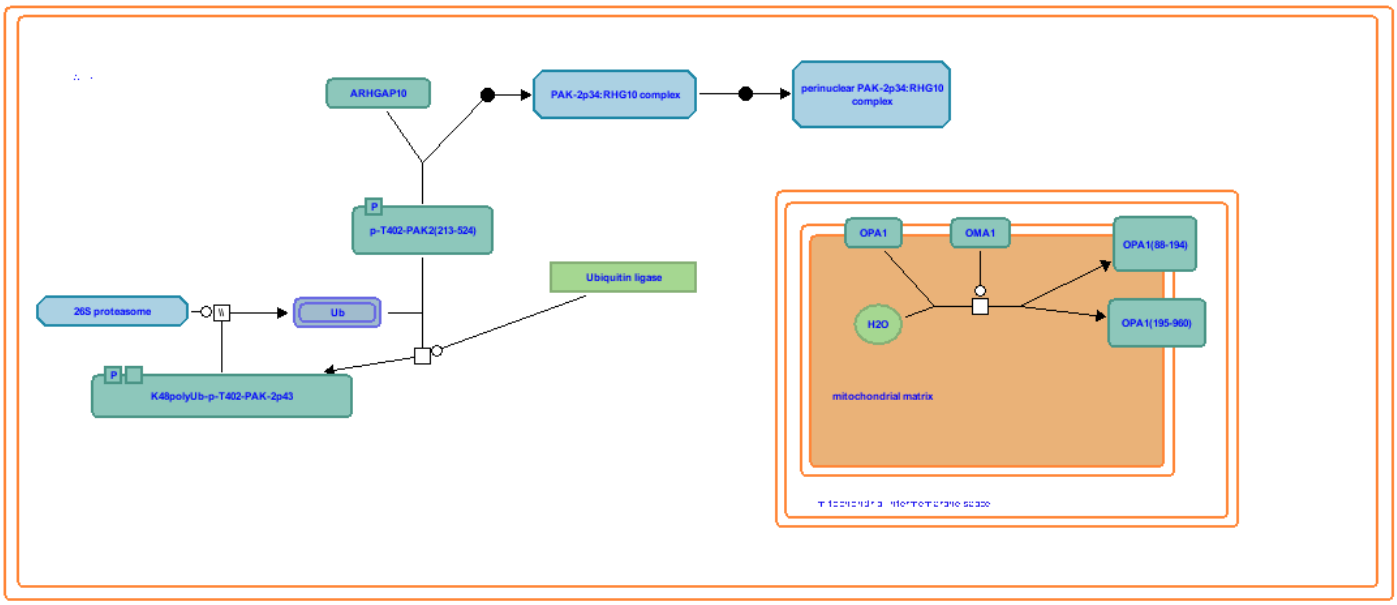
Liu P,Cheng H,Roberts TM,Zhao JJ, "Targeting the phosphoinositide 3-kinase pathway in cancer", Nat Rev Drug Discov, 8, 2009, 627-44.

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

Huang CH,Mandelker D,Schmidt-Kittler O,Samuels Y,Velculescu VE,Kinzler KW,Vogelstein B,Gabelli SB,Amzel LM, "The structure of a human p110alpha/p85alpha complex elucidates the effects of oncogenic PI3Kalpha mutations", Science, 318, 2007, 1744-8.

Zhao JJ,Liu Z,Wang L,Shin E,Loda MF,Roberts TM, "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.

2.36. Signaling by PTK6 (R-HSA-8848021)



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	P56945	P04626	P00533	P01116	P21860
P40763	P22681	Q14185	Q9NRY4		

Authors

Bevan A Paul,003-07-31

Reviewers

Croft David,017-12-04

References

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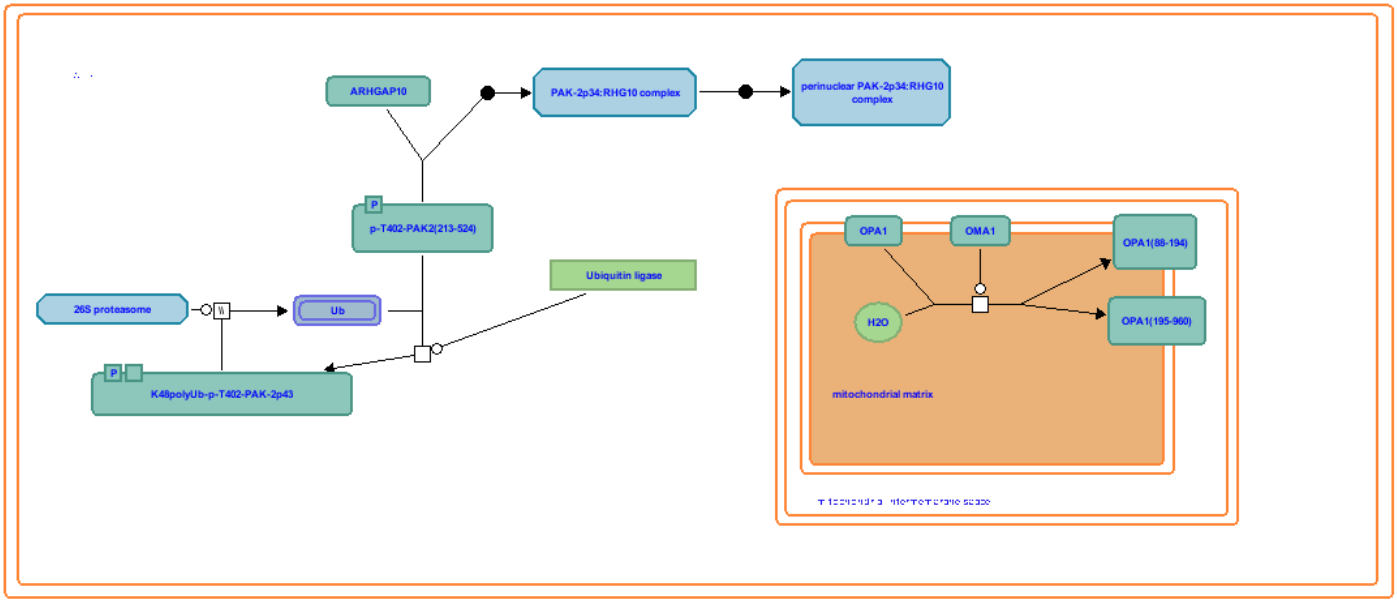
Shepherd PR,Withers DJ,Siddle K, "Phosphoinositide 3-kinase: the key switch mechanism in insulin signalling.", Biochem J, 333, 1998, 471-90.

2.37. Signaling by Non-Receptor Tyrosine Kinases (R-HSA-9006927)



Summation

species name:Homo sapiens,The ability of growth factors to protect from apoptosis is primarily due to the activation of the AKT survival pathway. P-I-3-kinase dependent activation of PDK leads to the activation of AKT which in turn affects the activity or expression of pro-apoptotic factors, which contribute to protection from apoptosis. AKT activation also blocks the activity of GSK-3b which could lead to additional antiapoptotic signals.

List of identifiers was found at this pathway

P01111	P56945	P04626	P00533	P01116	P21860
P40763	P22681	Q14185	Q9NRY4		

Authors

de Bono Bernard,007-01-10

Editors

Jupe Steve,010-02-03

Reviewers

Croft David,017-12-04

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Kamei T,Jones SR,Chapman BM,MCGonigle KL,Dai G,Soares MJ, "The phosphatidylinositol 3-kinase/Akt signaling pathway modulates the endocrine differentiation of trophoblast cells", Mol Endocrinol, 16, 2002, 1469-81.

Eswarakumar VP,Lax I,Schlessinger J, "Cellular signaling by fibroblast growth factor receptors", Cytokine Growth Factor Rev, 16, 2005, 139-49.

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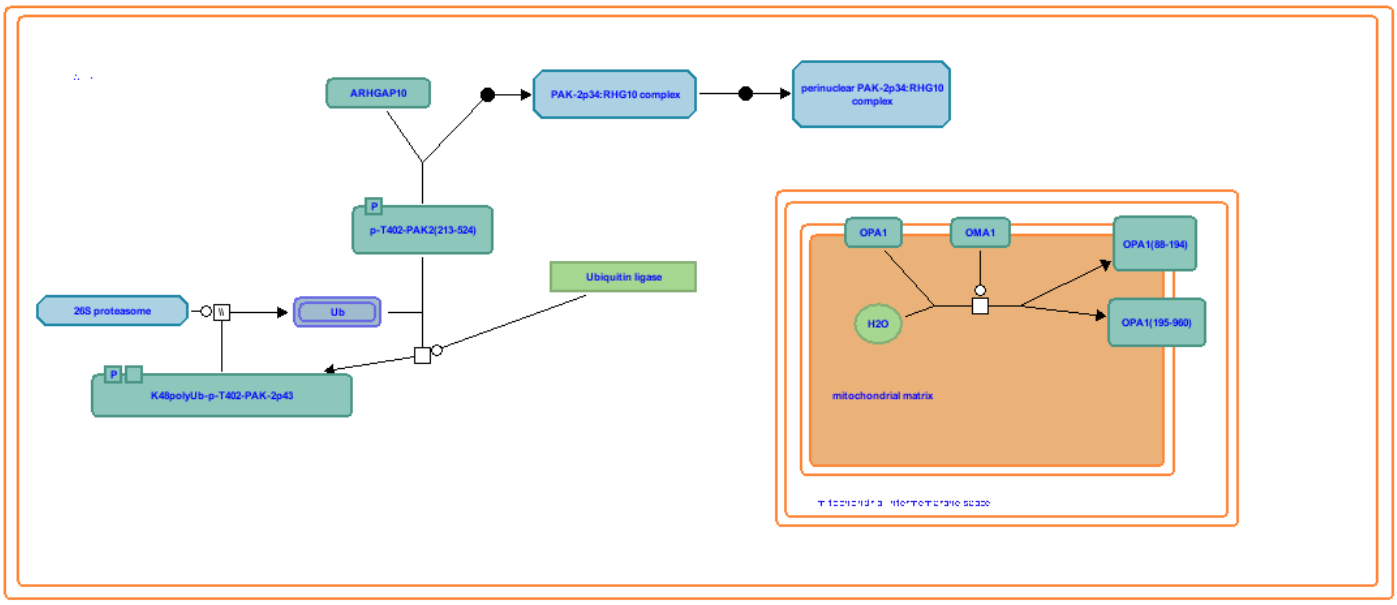
2.38. Interleukin-4 and 13 signaling (R-HSA-6785807)



Summation

species name:Homo sapiens,Syndecans are type I transmembrane proteins, with an N-terminal ectodomain that contains several consensus sequences for glycosaminoglycan (GAG) attachment and a short C-terminal cytoplasmic domain. Syndecan-1 and -3 GAG attachment sites occur in two distinct clusters, one near the N-terminus and the other near the membrane-attachment site, separated by a proline and threonine-rich 'spacer'. Syndecan ectodomain sequences are poorly conserved in the family and between species, but the transmembrane and cytoplasmic domains are highly conserved. Syndecan-1 and -3 form a subfamily. Syndecan core proteins form dimers (Choi et al. 2007) and at least syndecan-3 and -4 form oligomers (Asundi & Carey 1995, Shin et al. 2012). Syndecan-1 is the major syndecan of epithelial cells including vascular endothelium. Syndecan-2 is present mostly in mesenchymal, neuronal and smooth muscle cells. Syndecan-3 is the major syndecan of the nervous system, while syndecan-4 is ubiquitously expressed but at lower levels than the other syndecans (refs in Alexopoulou et al. 2007). The core syndecan protein has three to five heparan sulfate or chondroitin sulfate chains, which interact with a variety of ligands including fibroblast growth factors, vascular endothelial growth factor, transforming growth factor-beta, fibronectin, collagen, vitronectin and several integrins. Syndecans may act as integrin coreceptors. Interactions between fibronectin and syndecans are modulated by tenascin-C.

Syndecans bind a wide variety of soluble and insoluble ligands, inckluding extracellular matrix components, cell adhesion molecules, growth factors, cytokines, and proteinases. As the cleaved ectodomains of syndecans retain the ability to bind ligands, ectodomain shedding is a mechanism for releasing soluble effectors that may compete for ligands with their cell-bound counterparts (Kainulainen et al. 1998). Shed ectodomains are found in inflammatory fluids (Subramanian et al. 1997) and may induce the proliferation of cancer cells (Maeda et al. 2004).

List of identifiers was found at this pathway

P08123	P04083	P40763	P27986	P42224	P10415
P14859	P07900	P04637	O43524	P02751	P11309
P05107	P23771	O15524	P37275		

Authors

Jupe Steve,012-07-31

Editors

Jupe Steve,013-04-26

Reviewers

Schmidt Esther,017-11-18

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Tkachenko E,Rhodes JM,Simons M, "Syndecans: new kids on the signaling block", Circ. Res., 96, 2005, 488-500.

Couchman JR, "Transmembrane signaling proteoglycans", Annu. Rev. Cell Dev. Biol., 26, 2010, 89-114.

2.39. Signaling by EGFRvIII in Cancer (R-HSA-5637812)

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

P07900 P01111 P00533 P01116 P42336 P27986 P22681

Authors

Orlic-Milacic Marija,015-12-22

Editors

Orlic-Milacic Marija,015-12-22

Reviewers

Croft David,017-12-04

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Clarke JH,Wang M,Irvine RF, "Localization, regulation and function of type II phosphatidylinositol 5-phosphate 4-kinases", Adv Enzyme Regul, 50, 2010, 12-8.

Clarke JH,Irvine RF, "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.

Clarke JH,Giudici ML,Burke JE,Williams RL,Maloney DJ,Marugan J,Irvine RF, "The function of phosphatidylinositol 5-phosphate 4-kinase Î³ (PI5P4KÎ³) explored using a specific inhibitor that targets the PI5P-binding site", Biochem. J., 466, 2015, 359-67.

2.40. Constitutive Signaling by EGFRvIII (R-HSA-5637810)

Summation

species name:Homo sapiens,compartment name:cytosol,The phosphorylated type 1 insulin-like growth factor receptor phosphorylates IR1, 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.

List of identifiers was found at this pathway

P07900 P01111 P00533 P01116 P42336 P27986 P22681

Authors

May Bruce,012-08-07

Editors

May Bruce,012-08-07

Reviewers

Croft David,017-12-04

References

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Siddle K, "Molecular basis of signaling specificity of insulin and IGF receptors: neglected corners and recent advances", Front Endocrinol (Lausanne), 3, 2012, 34.

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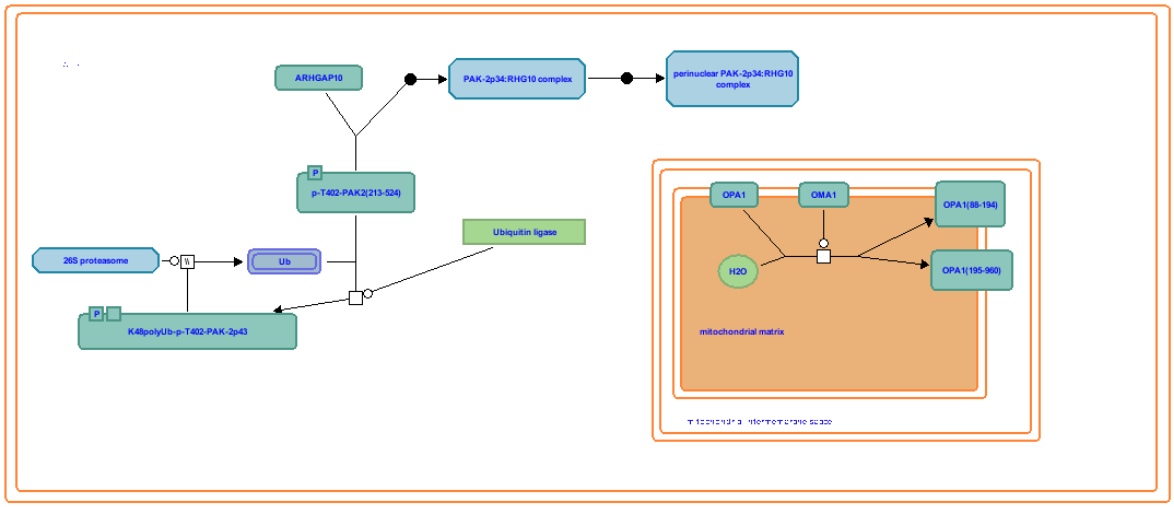
Annunziata M,Granata R,Ghigo E, "The IGF system", Acta Diabetol, 48, 2011, 1-9.

2.41. Syndecan interactions (R-HSA-3000170)



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

P02452 P05106 P17252 P02751 P08123 P24821 P02461

Authors

Bevan A Paul,003-07-31

Editors

Schmidt Esther,017-11-16

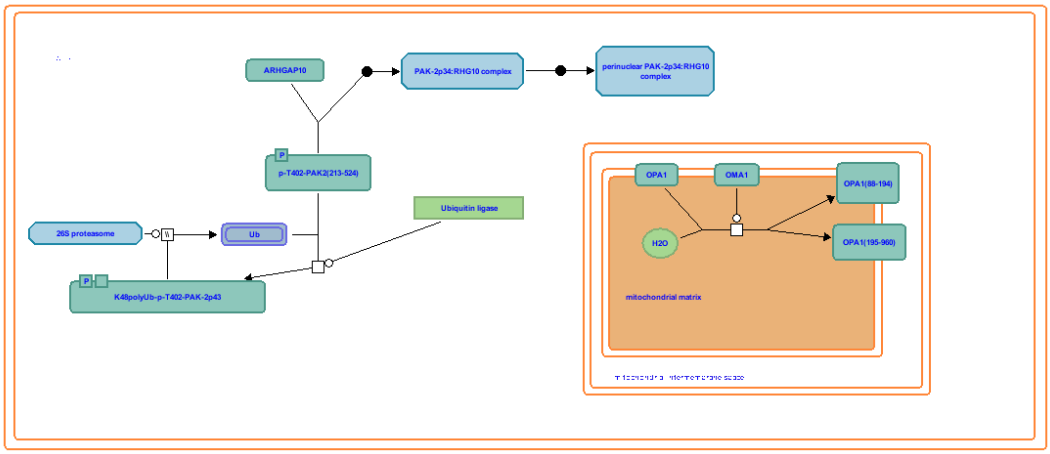
Reviewers

Croft David,017-12-04

References

White MF,Kahn CR, "The insulin signaling system.", J Biol Chem, 269, 1994, 1-4.

2.42. Signaling by Interleukins (R-HSA-449147)



Summation

species name:Homo sapiens,Signaling via FGFRs is mediated via direct recruitment of signaling proteins that bind to tyrosine auto-phosphorylation sites on the activated receptor and via closely linked docking proteins that become tyrosine phosphorylated in response to FGF-stimulation and form a complex with additional complement of signaling proteins. The activation loop in the catalytic domain of FGFR maintains the PTK domain in an inactive or low activity state. The activation-loop of FGFR1, for instance, contains two tyrosine residues that must be autophosphorylated for maintaining the catalytic domain in an active state. In the autoinhibited configuration, a kinase invariant proline residue at the C-terminal end of the activation loop interferes with substrate binding while allowing access to ATP in the nucleotide binding site.In addition to the catalytic PTK core, the cytoplasmic domain of FGFR contains several regulatory sequences. The juxtamembrane domain of FGFRs is considerably longer than that of other receptor tyrosine kinases. This region contains a highly conserved sequence that serves as a binding site for the phosphotyrosine binding (PTB) domain of FRS2. A variety of signaling proteins are phosphorylated in response to FGF stimulation, including Shc, phospholipase-C gamma and FRS2 leading to stimulation of intracellular signaling pathways that control cell proliferation, cell differentiation, cell migration, cell survival and cell shape.

List of identifiers was found at this pathway

P51812	Q13126	P08123	Q13164	P04083	P40763
P27986	P42224	P10415	P14859	P07900	P35568
Q06124	P04637	P07948	Q14738	Q9UHD2	O43524
P45984	P02751	P11309	P05107	P42336	P23771
P22681	O15524	P37275			

Authors

de Bono Bernard,007-01-10

Editors

Jupe Steve,010-02-03

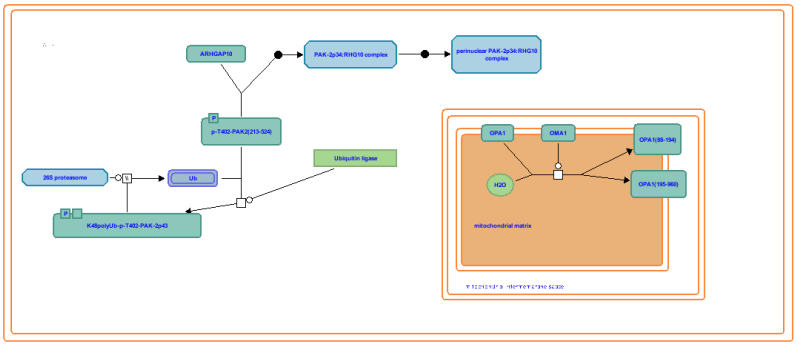
Reviewers

Schmidt Esther,017-11-18

References

Mohammadi M,Schlessinger J,Hubbard SR, "Structure of the FGF receptor tyrosine kinase domain reveals a novel autoinhibitory mechanism", Cell, 86, 1996, 577-87.

2.43. PI-3K cascade:FGFR2 (R-HSA-5654695)



Summation

species name:Homo sapiens,compartment name:plasma membrane,All ERBB2 heterodimers, ERBB2:EGFR, ERBB2:ERBB3 and ERBB2:ERBB4, are able to activate RAF/MAP kinase cascade by recruiting SHC1 (Pinkas-Kramarski et al. 1996, Sepp-Lorenzino et al. 1996) to phosphorylated C-tail tyrosine residues in either EGFR (Y1148 and Y1173), ERBB2 (Y1196, Y1221, Y1222 and Y1248), ERBB3 (Y1328) or ERBB4 (Y1188 and Y1242 in JM-A CYT1 isoform, Y1178 and Y1232 in JM-B CYT1 isoform, Y1172 and Y1226 in JM-A CYT2 isoform). SHC1 recruitment is followed by phosphorylation (Segatto et al. 1993, Soler et al. 1994), and the phosphorylated SHC1 recruits GRB2:SOS1 complex (Xie et al. 1995), which leads to SOS1-mediated guanyl-nucleotide exchange on RAS (Xie et al. 1995) and downstream activation of RAF and MAP kinases.

List of identifiers was found at this pathway

P21802 P42336 Q06124 P27986

Authors

Orlic-Milacic Marija,011-11-04

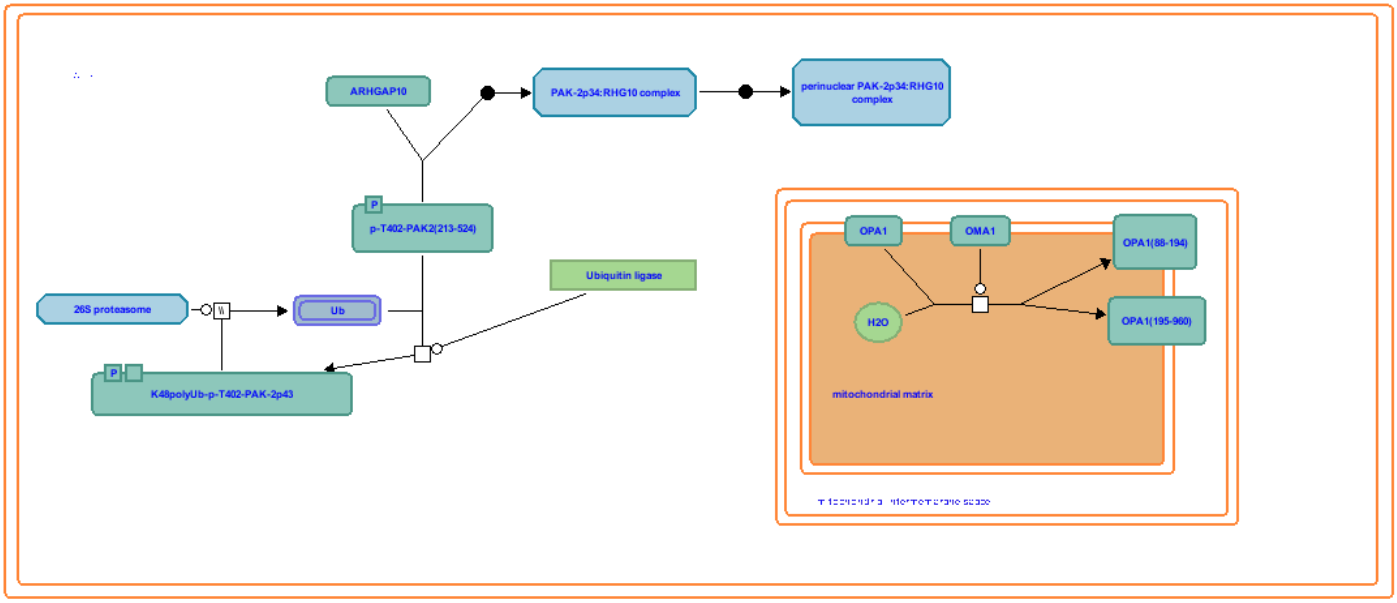
Editors

Matthews Lisa,011-11-07
D'Eustachio Peter,011-11-07

Reviewers

Croft David,017-12-04

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



Summation

species name:Homo sapiens,disease name:disease,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.

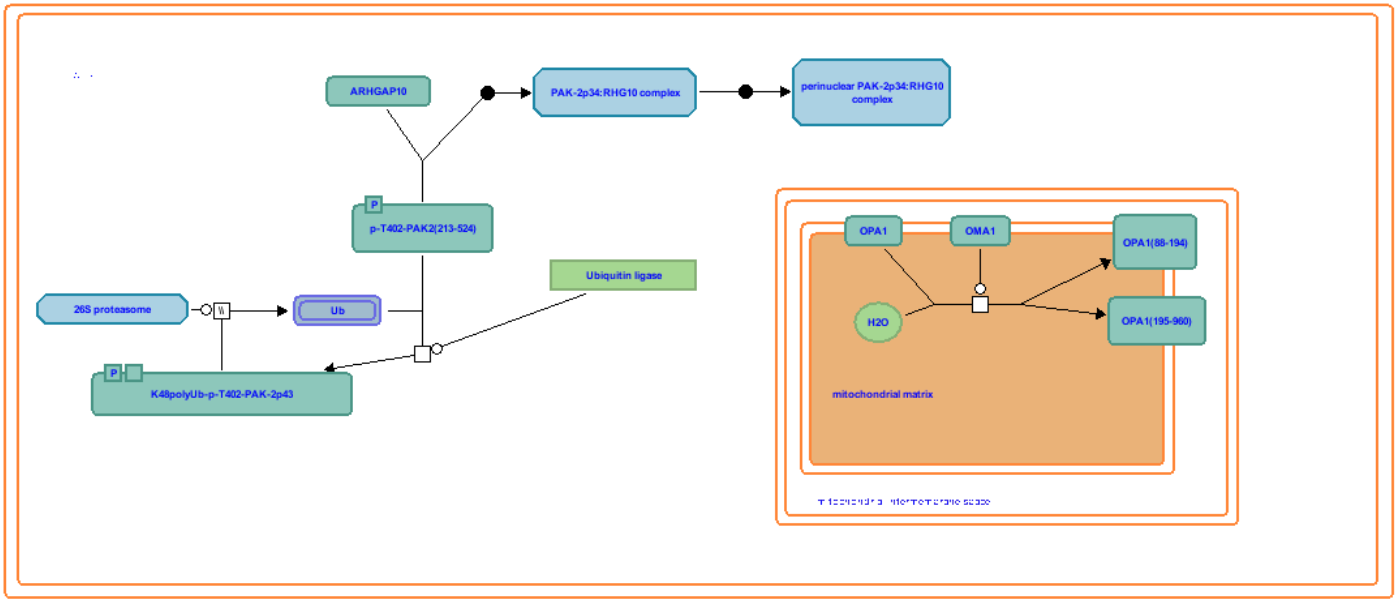
List of identifiers was found at this pathway

P55211 P98177 P49815 Q00987 P42345 O43524

Reviewers

Varusai Thawfeek,017-07-25

2.45. Axon guidance (R-HSA-422475)



Summation

species name:Homo sapiens,compartment name:cytosol,ERBB2, also known as HER2 or NEU, is a receptor tyrosine kinase (RTK) belonging to the EGFR family. ERBB2 possesses an extracellular domain that does not bind any known ligand, contrary to other EGFR family members, a single transmembrane domain, and an intracellular domain consisting of an active kinase and a C-tail with multiple tyrosine phosphorylation sites. Inactive ERBB2 is

associated with a chaperone heat shock protein 90 (HSP90) and its co-chaperone CDC37 (Xu et al. 2001, Citri et al. 2004, Xu et al. 2005). In addition, ERBB2 is associated with ERBB2IP (also known as ERBIN or LAP2), a protein responsible for proper localization of ERBB2. In epithelial cells, ERBB2IP restricts expression of ERBB2 to basolateral plasma membrane regions (Borg et al. 2000).
ERBB2 becomes activated by forming a heterodimer with another ligand-activated EGFR family member, either EGFR, ERBB3 or ERBB4, which is accompanied by dissociation of chaperoning proteins HSP90 and CDC37 (Citri et al. 2004), as well as ERBB2IP (Borg et al. 2000) from ERBB2. ERBB2 heterodimers function to promote cell proliferation, cell survival and differentiation, depending on the cellular context. ERBB2 can also be activated by homodimerization when it is overexpressed, in cancer for example.
In cells expressing both ERBB2 and EGFR, EGF stimulation of EGFR leads to formation of both ERBB2:EGFR heterodimers (Wada et al. 1990, Karunagaran et al. 1996) and EGFR homodimers. Heterodimers of ERBB2 and EGFR trans-autophosphorylate on twelve tyrosine residues, six in the C-tail of EGFR and six in the C-tail of ERBB2 - Y1023, Y1139, Y1196, Y1221, Y1222 and Y1248 (Margolis et al. 1989, Hazan et al. 1990,Walton et al. 1990, Helin et al. 1991, Ricci et al. 1995, Pinkas-Kramarski 1996). Phosphorylated tyrosine residues in the C-tail of EGFR and ERBB2 serve as docking sites for downstream signaling molecules. Three key signaling pathways activated by ERBB2:EGFR heterodimers are RAF/MAP kinase cascade, PI3K-induced AKT signaling, and signaling by phospholipase C gamma (PLCG1). Downregulation of EGFR signaling is mediated by ubiquitin ligase CBL, and is shown under Signaling by EGFR.
In cells expressing ERBB2 and ERBB3, ERBB3 activated by neuregulin NRG1 or NRG2 binding (Tzahar et al. 1994) forms a heterodimer with ERBB2 (Pinkas-Kramarski et al. 1996, Citri et al. 2004). ERBB3 is the only EGFR family member with no kinase activity, and can only function in heterodimers, with ERBB2 being its preferred heterodimerization partner. After heterodimerization, ERBB2 phosphorylates ten tyrosine residues in the C-tail of ERBB3, Y1054, Y1197, Y1199, Y1222, Y1224, Y1260, Y1262, Y1276, Y1289 and Y1328 (Prigent et al. 1994, Pinkas-Kramarski et al. 1996, Vijapurkar et al. 2003, Li et al. 2007) that subsequently serve as docking sites for downstream signaling molecules, resulting in activation of PI3K-induced AKT signaling and RAF/MAP kinase cascade. Signaling by ERBB3 is downregulated by the action of RNF41 ubiquitin ligase, also known as NRDP1.
In cells expressing ERBB2 and ERBB4, ligand stimulated ERBB4 can either homodimerize or form heterodimers with ERBB2 (Li et al. 2007), resulting in trans-autophosphorylation of ERBB2 and ERBB4 on C-tail tyrosine residues that will subsequently serve as docking sites for downstream signaling molecules, leading to activation of RAF/MAP kinase cascade and, in the case of ERBB4 CYT1 isoforms, PI3K-induced AKT signaling (Hazan et al. 1990, Cohen et al. 1996, Li et al. 2007, Kaushansky et al. 2008). Signaling by ERBB4 is downregulated by the action of WWP1 and ITCH ubiquitin ligases, and is shown under Signaling by ERBB4.

List of identifiers was found at this pathway

P01111	P51812	P04626	P01116	Q13164	P27986
P02461	P07900	Q06124	P07948	P17252	O00533
O43602	P11362	P05106	Q99490	O15264	P00533
P08581	P42336	Q9HAU5	Q99435	Q14185	Q9NRY4
P52735	P12110				

Authors

Orlic-Milacic Marija,011-11-04

Editors

Matthews Lisa,011-11-07

D'Eustachio Peter,011-11-07

Reviewers

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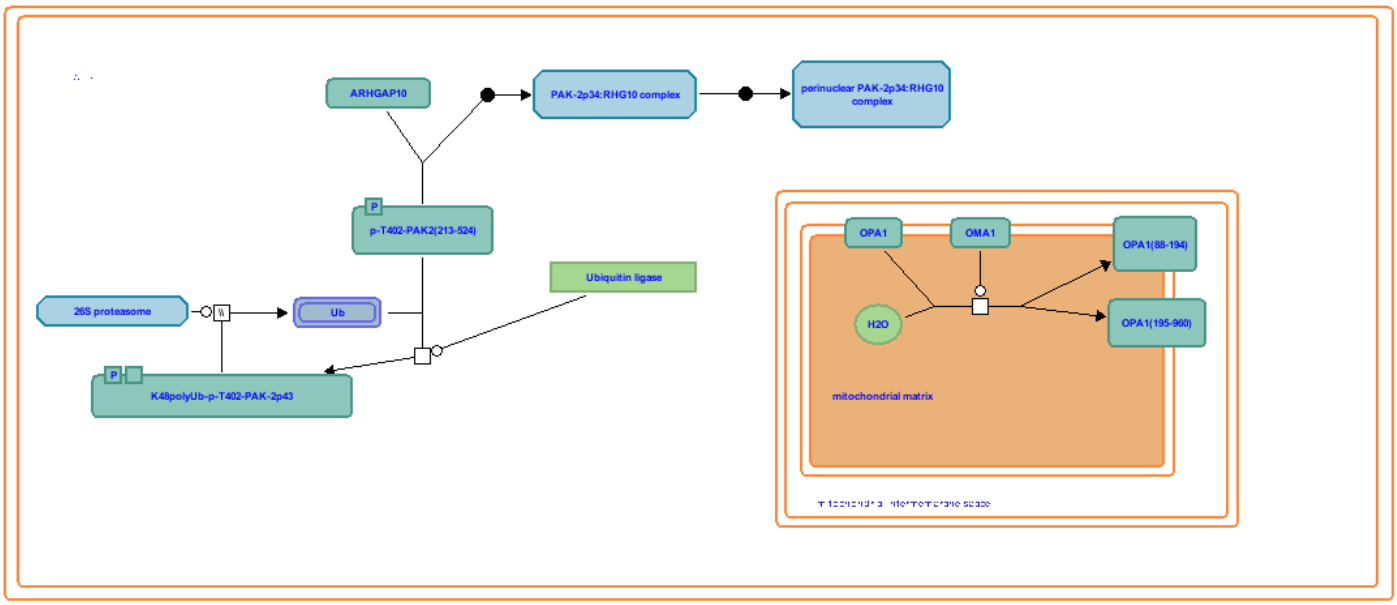
2.46. Cytokine Signaling in Immune system (R-HSA-1280215)



Summation

species name:Homo sapiens,disease name: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).

List of identifiers was found at this pathway

P27986	P42224	P10415	P40763	P14859	P51812
P35568	Q06124	Q9UHD2	P07900	P07948	P04637
P02751	P42336	P23771	P22681	P45984	Q13164
Q13126	O00300	Q9C040	P08123	P04083	P29590
Q05655	Q14738	O43524	P11309	P05107	P52292
O15524	P37275	O75382			

Authors

Orlic-Milacic Marija,012-07-18

Reviewers

Croft David,017-12-04

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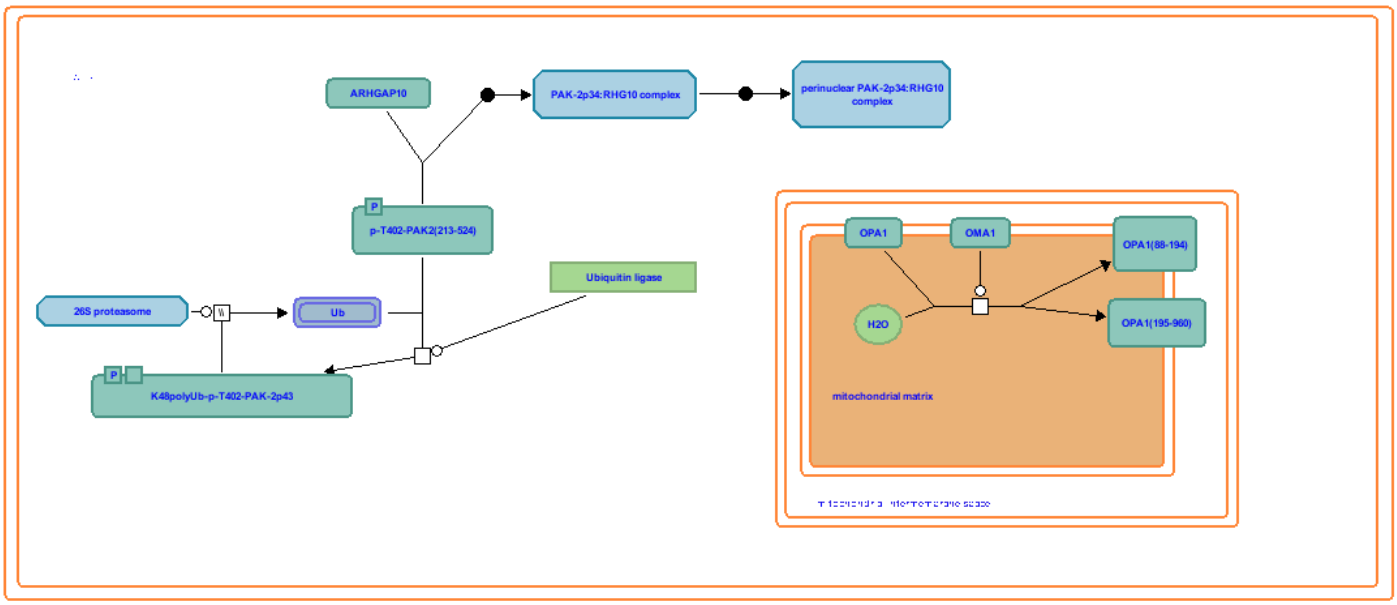
Zhao JJ,Liu Z,Wang L,Shin E,Loda MF,Roberts TM, "The oncogenic properties of mutant p110alpha and p110beta phosphatidylinositol 3-kinases in human mammary epithelial cells", Proc. Natl. Acad. Sci. U.S.A., 102, 2005, 18443-8.

Miled N,Yan Y,Hon WC,Perisic O,Zvelebil M,Inbar Y,Schneidman-Duhovny D,Wolfson HJ,Backer JM,Williams RL, "Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit", Science, 317, 2007, 239-42.

Horn S,Bergholz U,Jücker M,McCubrey JA,Trümper L,Stocking C,Bäsecke J, "Mutations in the catalytic subunit of class IA PI3K confer leukemogenic potential to hematopoietic cells", Oncogene, 27, 2008, 4096-106.

Sun M,Hillmann P,Hofmann BT,Hart JR,Vogt PK, "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.

2.47. FRS-mediated FGFR2 signaling (R-HSA-5654700)



Summation

species name:Homo sapiens,PTK6 (BRK) is an oncogenic non-receptor tyrosine kinase that functions downstream of ERBB2 (HER2) (Xiang et al. 2008, Peng et al. 2015) and other receptor tyrosine kinases, such as EGFR (Kamalati et al. 1996) and MET (Castro and Lange 2010). Since ERBB2 forms heterodimers with EGFR and since MET can heterodimerize with both ERBB2 and EGFR (Tanizaki et al. 2011), it is not clear if MET and EGFR activate PTK6 directly or act through ERBB2. Levels of PTK6 increase under hypoxic conditions (Regan Anderson et al. 2013, Pires et al. 2014). The kinase activity of PTK6 is negatively regulated by PTPN1 phosphatase (Fan et al. 2013) and SRMS kinase (Fan et al. 2015), as well as the STAT3 target SOCS3 (Gao et al. 2012).PTK6 activates STAT3-mediated transcription (Ikeda et al. 2009, Ikeda et al. 2010) and may also activate STAT5-mediated transcription (Ikeda et al. 2011). PTK6 promotes cell motility and

migration by regulating the activity of RHO GTPases RAC1 (Chen et al. 2004) and RHOA (Shen et al. 2008), and possibly by affecting motility-related kinesins (Lukong and Richard 2008). PTK6 crosstalks with AKT1 (Zhang et al. 2005, Zheng et al. 2010) and RAS signaling cascades (Shen et al. 2008, Ono et al. 2014) and may be involved in MAPK7 (ERK5) activation (Ostrander et al. 2007, Zheng et al. 2012). PTK6 enhances EGFR signaling by inhibiting EGFR down-regulation (Kang et al. 2010, Li et al. 2012, Kang and Lee 2013). PTK6 may also enhance signaling by IGF1R (Fan et al. 2013) and ERBB3 (Kamalati et al. 2000).PTK6 promotes cell cycle progression by phosphorylating and inactivating CDK inhibitor CDKN1B (p27) (Patel et al. 2015).PTK6 activity is upregulated in osteopontin (OPN or SPP1)-mediated signaling, leading to increased VEGF expression via PTK6/NF-kappaB/ATF4 signaling path. PTK6 may therefore play a role in VEGF-dependent tumor angiogenesis (Chakraborty et al. 2008).PTK6 binds and phosphorylates several nuclear RNA-binding proteins, including SAM68 family members (KHDRSB1, KHDRSB2 and KHDRSB3) (Derry et al. 2000, Haegebarth et al. 2004, Lukong et al. 2005) and SFPQ (PSF) (Lukong et al. 2009). The biological role of PTK6 in RNA processing is not known.For a review of PTK6 function, please refer to Goel and Lukong 2015.

List of identifiers was found at this pathway

P21802 P01111 Q06124 P01116

Authors

Orlic-Milacic Marija,016-01-05

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Orlic-Milacic Marija,016-01-05

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Schmidt Esther,017-11-18

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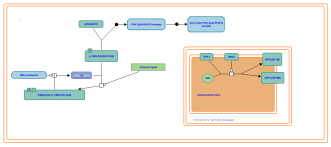
Kamalati T,Jolin HE,Fry MJ,Crompton MR, "Expression of the BRK tyrosine kinase in mammary epithelial cells enhances the coupling of EGF signalling to PI 3-kinase and Akt, via erbB3 phosphorylation", Oncogene, 19, 2000, 5471-6.

Castro NE,Lange CA, "Breast tumor kinase and extracellular signal-regulated kinase 5 mediate Met receptor signaling to cell migration in breast cancer cells", Breast Cancer Res., 12, 2010, R60.

2.48. Signaling by FGFR2 (R-HSA-5654738)



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

P01111 P21802 Q06124 P01116 P42336 P27986 P22681

Authors

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Croft David,017-12-04

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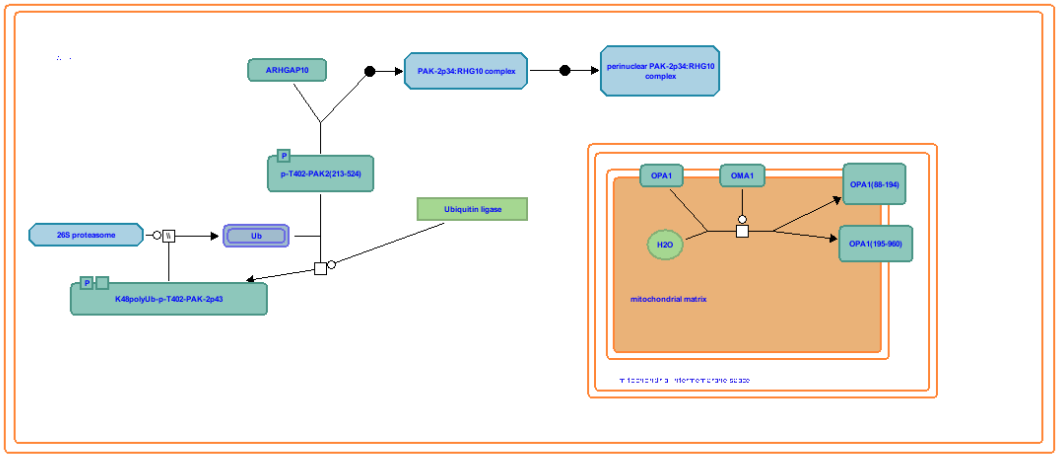
Fredriksson L,Li H,Eriksson U, "The PDGF family: four gene products form five dimeric isoforms", Cytokine Growth Factor Rev, 15, 2004, 197-204.

2.49. SHC1 events in ERBB2 signaling (R-HSA-1250196)



Summation

species name:Homo sapiens,The PI3K (Phosphatidlyinositol-3-kinase) - AKT signaling pathway stimulates cell growth and survival.

List of identifiers was found at this pathway

P01111 Q05655 P17252 P04626 P00533 P01116 P21860

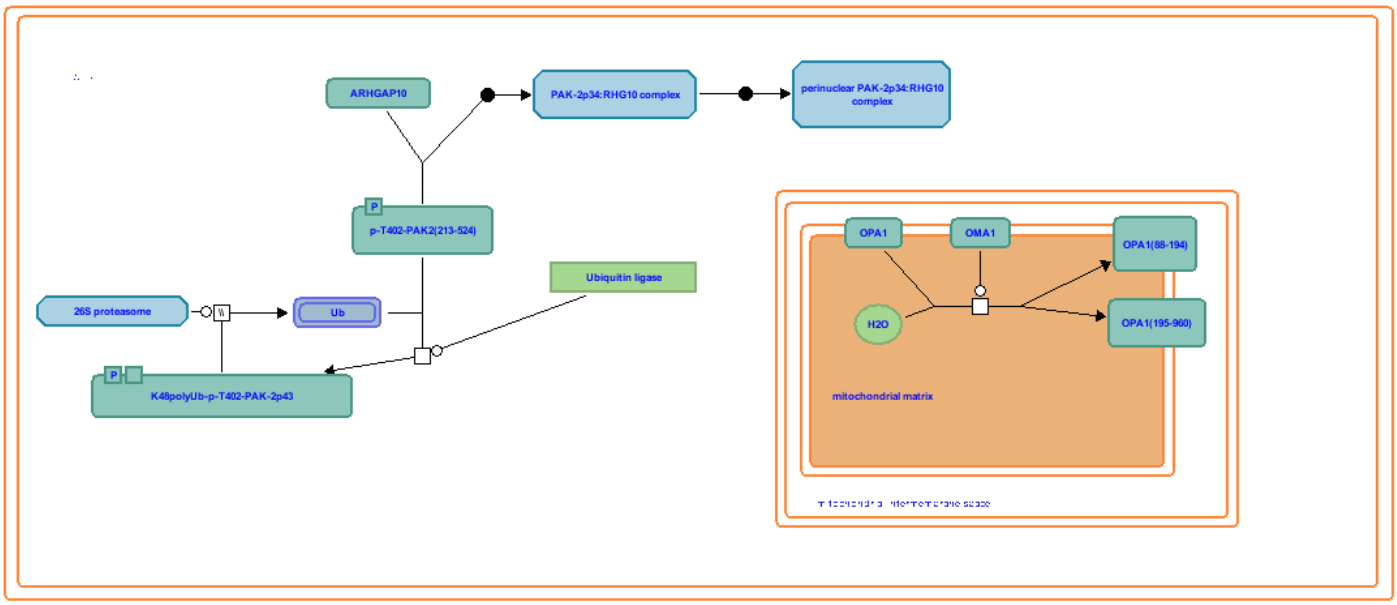
Reviewers

Croft David,017-12-04

References

Downward J, "PI 3-kinase, Akt and cell survival", Semin. Cell Dev. Biol., 15, 2004, 177-82.

2.50. NGF signalling via TRKA from the plasma membrane (R-HSA-187037)



Summation

species name:Homo sapiens,Platelet activation begins with the initial binding of adhesive ligands and of the excitatory platelet agonists (released or generated at the sites of vascular trauma) to cognate receptors on the platelet membrane (Ruggeri 2002). Intracellular signaling reactions then enhance the adhesive and procoagulant properties of tethered platelets or of platelets circulating in the proximity. Once platelets have adhered they degranulate, releasing stored secondary agents such as ADP, ATP, and synthesize thromboxane A2. These amplify the response, activating and recruiting further platelets to the area and promoting platelet aggregation. These amplify the response, activating and recruiting further platelets to the area and promoting platelet aggregation. Adenosine nucleotides signal through P2 purinergic receptors on the platelet membrane. ADP activates P2Y1 and P2Y12, which signal via both the alpha and gamma:beta components of the heterotrimeric G-protein (Hirsch et al. 2001, 2006),
while ATP activates the ionotropic P2X1 receptor (Kunapuli et al. 2003). Activation of these

receptors initiates a complex signaling cascade that ultimately results in platelet activation, aggregation and thrombus formation (Kahner et al. 2006).

Integrin AlphaIIbBeta3 is the most abundant platelet receptor, with 40 000 to 80 000 copies per resting platelet, acting as a major receptor for fibrinogen and other adhesive molecules (Wagner et al. 1996). Activation of AlphaIIbBeta3 enhances adhesion and leads to platelet-platelet interactions, and thus aggregation (Philips et al. 1991). GP VI is the most potent collagen receptor initiating signal generation, an ability derived from its interaction with the FcRI gamma chain. This results in the phosphorylation of the gamma-chain by non-receptor tyrosine kinases of the Src family (1). The phosphotyrosine motif is recognized by the SH2 domains of Syk, a tyrosine kinase. This association activates the Syk enzyme, leading to activation (by tyrosine phosphorylation) of PLC gamma2 (2). Thrombin is an important platelet agonist generated on the membrane of stimulated platelets. Thrombin acts via cell surface Protease Activated Receptors (PARs). PARs are G-protein coupled receptors activated by a proteolytic cleavage in an extracellular loop (Vu, 1991) (3). Activated PARs signal via G alpha q (4) and via the beta:gamma component of the G-protein (5). Both stimulate PLC giving rise to PIP2 hydrolysis and consequent activation of PI3K (6). PLCgamma2 activation also gives rise to IP3 (7) which stimulates the IP3 receptor (8) leading to increased intracellular calcium. Platelet activation further results in the scramblase-mediated transport of negatively-charged phospholipids to the platelet surface. These phospholipids provide a catalytic surface (with the charge provided by phosphatidylserine and phosphatidylethanolamine) for the tenase complex (formed by the activated forms of the blood coagulation factors factor VIII and factor I).

List of identifiers was found at this pathway

P01111	P51812	O15264	P01116	Q13164	P40763
P42336	P27986	P35568	Q14738		

Authors

de Bono Bernard,004-08-13

Reviewers

Schmidt Esther,017-11-18

References

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Vu TK,Hung DT,Wheaton VI,Coughlin SR, "Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation", Cell, 64, 1991, 1057-68.

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Kunapuli SP,Dorsam RT,Kim S,Quinton TM, "Platelet purinergic receptors", Curr Opin Pharmacol, 3, 2003, 175-80.

3. Identifiers was found.

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Identifiers	mapsTo	Resource	Identifiers	mapsTo	Resource
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Q13635	Q13635	UNIPROT	P15529	P15529	UNIPROT
Q99490	Q99490	UNIPROT	Q9UPN9	Q9UPN9	UNIPROT
O00300	O00300	UNIPROT	P51587	P51587	UNIPROT
P11168	P11168	UNIPROT	O75382	O75382	UNIPROT
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P04083	P04083	UNIPROT	P08684	P08684	UNIPROT
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P46940	P46940	UNIPROT	Q92574	Q92574	UNIPROT
P27986	P27986	UNIPROT	P49815	P49815	UNIPROT
Q13485	Q13485	UNIPROT	Q9UHW9	Q9UHW9	UNIPROT
P01111	P01111	UNIPROT	Q13126	Q13126	UNIPROT
P04921	P04921	UNIPROT	O43602	O43602	UNIPROT
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Q99081	Q99081	UNIPROT	P37275	P37275	UNIPROT
P16234	P16234	UNIPROT	O15528	O15528	UNIPROT
P46531	P46531	UNIPROT	P52292	P52292	UNIPROT
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P17252	P17252	UNIPROT	P21860	P21860-1	UNIPROT
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O14746	O14746	UNIPROT	P40763	P40763	UNIPROT
Q13444	Q13444	UNIPROT	P04843	P04843	UNIPROT
P49454	P49454	UNIPROT	P09619	P09619	UNIPROT
O43524	O43524	UNIPROT	O00750	O00750	UNIPROT
P10721	P10721	UNIPROT	P35568	P35568	UNIPROT
O60934	O60934	UNIPROT	Q9BZL6	Q9BZL6	UNIPROT
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Q99435	Q99435	UNIPROT	Q00987	Q00987	UNIPROT
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P42771	Q8N726	UNIPROT	P02751	P02751	UNIPROT
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P05106	P05106	UNIPROT	P54278	P54278	UNIPROT
P98177	P98177-1, P98177-2	UNIPROT	P05107	P05107	UNIPROT
P10415	P10415	UNIPROT	Q15119	Q15119	UNIPROT
O15066	O15066	UNIPROT	P14859	P14859	UNIPROT
Q9UHD2	Q9UHD2	UNIPROT	Q96L34	Q96L34	UNIPROT
P78527	P78527	UNIPROT	O60346	O60346	UNIPROT
Q9Y4A5	Q9Y4A5	UNIPROT	P08581	P08581	UNIPROT
P02788	P02788	UNIPROT	Q6NUQ1	Q6NUQ1	UNIPROT

Identifiers	mapsTo	Resource	Identifiers	mapsTo	Resource
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P82987	P82987	UNIPROT	Q9NQC7	Q9NQC7	UNIPROT
P09958	P09958	UNIPROT	P27540	P27540	UNIPROT
P49674	P49674	UNIPROT	Q9C040	Q9C040	UNIPROT
Q7Z5R6	Q7Z5R6	UNIPROT	Q86UP2	Q86UP2	UNIPROT
O00533	O00533	UNIPROT	P11362	P11362, P11362-19, P11362-1	UNIPROT
P40692	P40692	UNIPROT	P37173	P37173	UNIPROT
P24821	P24821	UNIPROT	P45984	P45984	UNIPROT
P21675	P21675	UNIPROT	P06213	P06213	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				