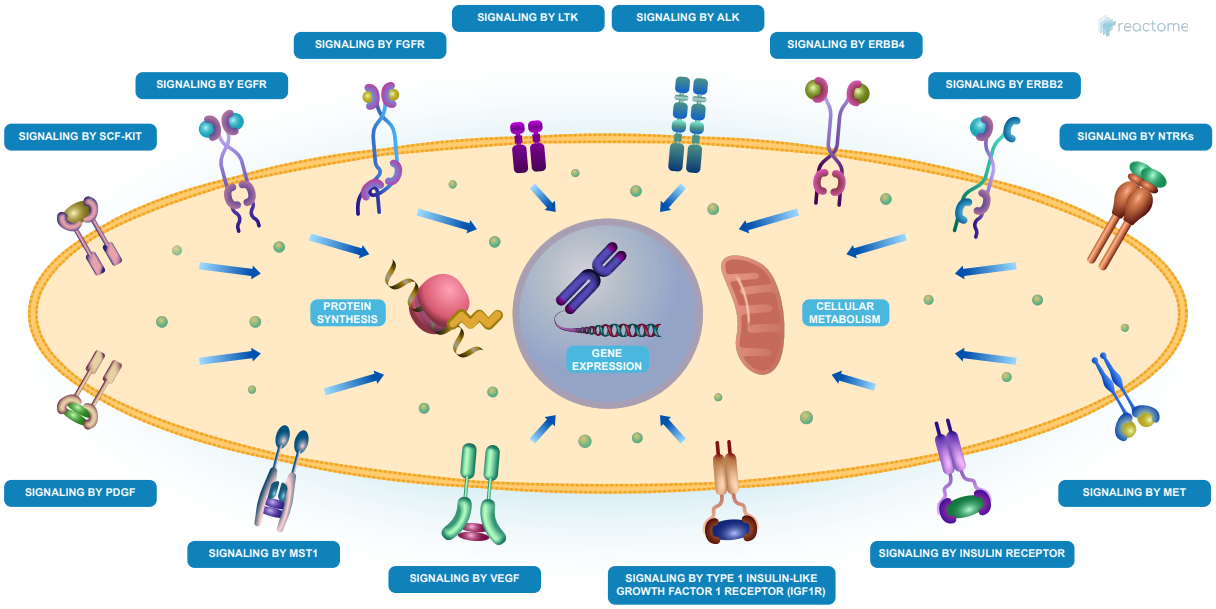
Signaling by Receptor Tyrosine Kinases



Annibali, D., Barroso, I., Bevan, AP., Birchmeier, W., Castagnoli, L., Claesson-Welsh, L., D'Eustachio, P., Earp HS, 3rd., Garapati, P V., Gotoh, N., Greene, LA., Harris, RC., Heldin, CH., Heynen, G., Hill, DP., Holzenberger, M., Inghirami, G., Jassal, B., Matthews, L., May, B., Misior, AM., Mohammadi, M., Muthuswamy, S., Nasi, S., Neckers, LM., Orlic-Milacic, M., Rothfels, K., Rönnstrand, L., Schmidt, EE., Stanley, FM., Stern, DF., Turner, S., Xu, W., Zeng, F., de Bono, B.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

27/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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

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

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

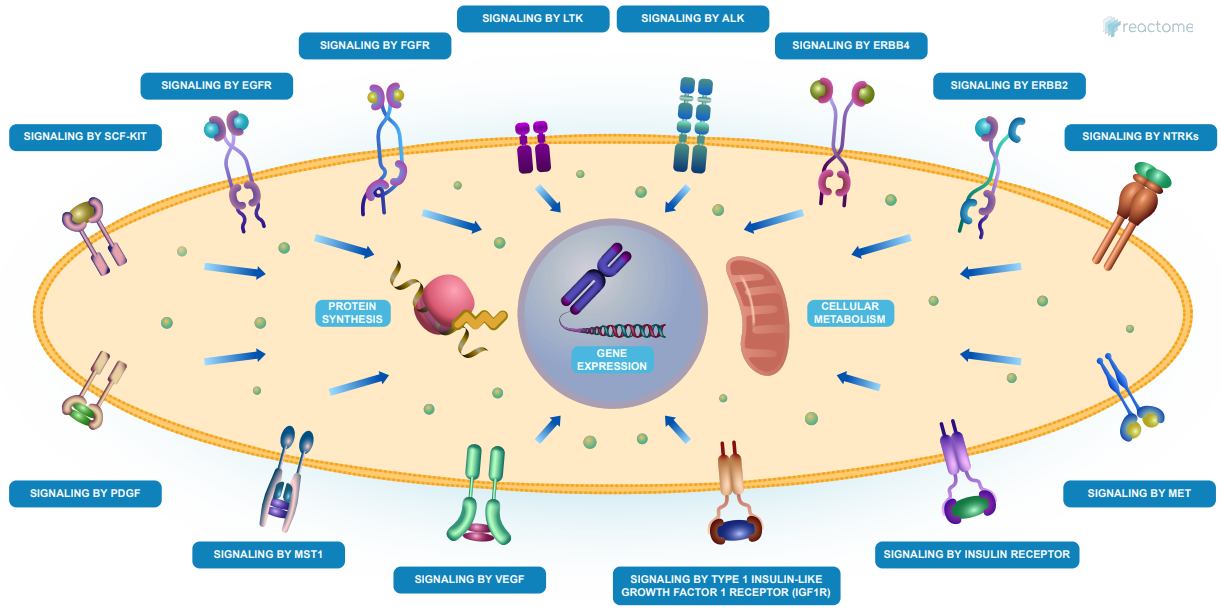
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 15 pathways (see Table of Contents)

Signaling by Receptor Tyrosine Kinases ↗

Stable identifier: R-HSA-9006934



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

Literature references

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

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

Manning, BD., Cantley, LC. (2007). AKT/PKB signaling: navigating downstream. *Cell, 129*, 1261-74. ↗

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

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

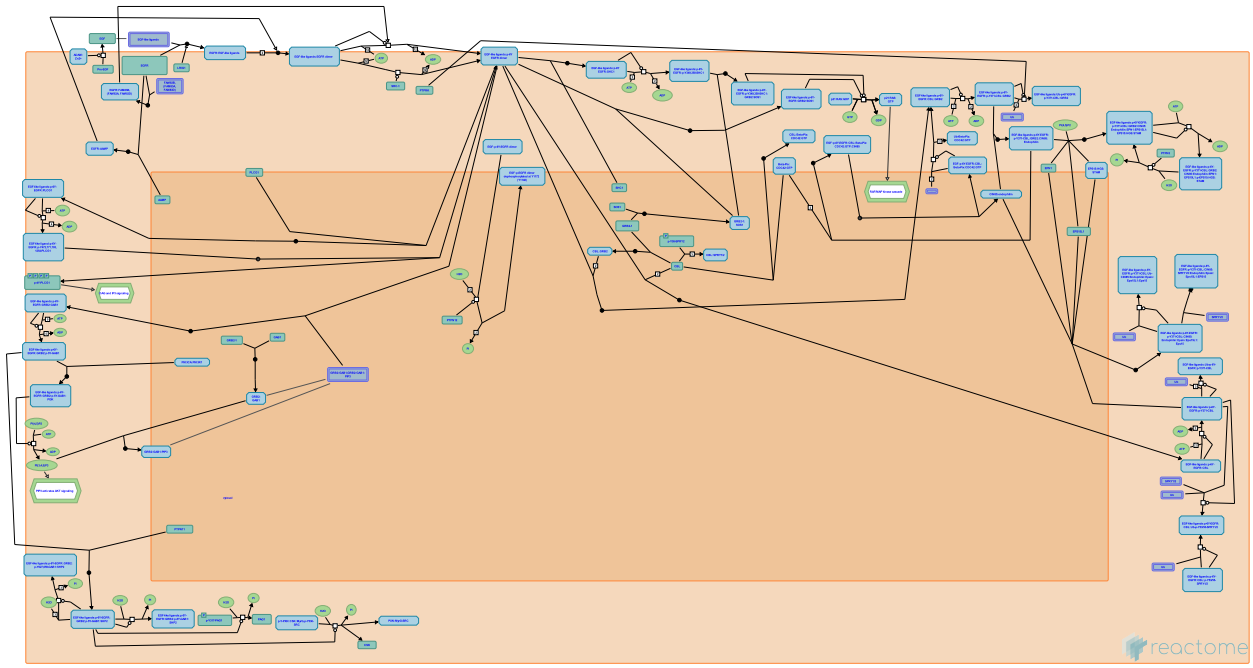
Editions

2017-05-24	Authored, Edited	Rothfels, K.
2017-06-22	Reviewed	D'Eustachio, P.
2023-10-13	Reviewed	D'Eustachio, P.

Signaling by EGFR ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-177929



The epidermal growth factor receptor (EGFR) is one member of the ERBB family of transmembrane glycoprotein tyrosine receptor kinases (RTK). Binding of EGFR to its ligands induces conformational change that unmasks the dimerization interface in the extracellular domain of EGFR, leading to receptor homo- or heterodimerization at the cell surface. Dimerization of the extracellular regions of EGFR triggers additional conformational change of the cytoplasmic EGFR regions, enabling the kinase domains of two EGFR molecules to achieve the catalytically active conformation. Ligand activated EGFR dimers trans-autophosphorylate on tyrosine residues in the cytoplasmic tail of the receptor. Phosphorylated tyrosines serve as binding sites for the recruitment of signal transducers and activators of intracellular substrates, which then stimulate intracellular signal transduction cascades that are involved in regulating cellular proliferation, differentiation, and survival. Recruitment of complexes containing GRB2 and SOS1 to phosphorylated EGFR dimers either directly, through phosphotyrosine residues that serve as GRB2 docking sites, or indirectly, through SHC1 recruitment, promotes GDP to GTP exchange on RAS, resulting in the activation of RAF/MAP kinase cascade. Binding of complexes of GRB2 and GAB1 to phosphorylated EGFR dimers leads to formation of the active PI3K complex, conversion of PIP2 into PIP3, and activation of AKT signaling. Phospholipase C-gamma1 (PLCG1) can also be recruited directly, through EGFR phosphotyrosine residues that serve as PLCG1 docking sites, which leads to PLCG1 phosphorylation by EGFR and activation of DAG and IP3 signaling. EGFR signaling is downregulated by the action of ubiquitin ligase CBL. CBL binds directly to the phosphorylated EGFR dimer through the phosphotyrosine Y1069 (i.e. Y1045 in the mature protein) in the C-tail of EGFR, and after CBL is phosphorylated by EGFR, it becomes active and ubiquitinates phosphorylated EGFR dimers, targeting them for degradation. Positive regulation of EGFR signaling by direct association of EGFR with accessory proteins such as AAMP and FAM83B is being investigated. For review of EGFR signaling, please refer to Carpenter 1999, Wells 1999, Schlessinger 2002, Herbst 2004, Avraham and Yarden, 2011, Bartel et al. 2016, Uribe et al. 2021, Keflee et al. 2022.

Literature references

Yarden, Y., Avraham, R. (2011). Feedback regulation of EGFR signalling: decision making by early and delayed loops. *Nat Rev Mol Cell Biol, 12*, 104-17. ↗

Cipriano, R., Jackson, MW., Bartel, CA., Parameswaran, N. (2016). FAM83 proteins: Fostering new interactions to drive oncogenic signaling and therapeutic resistance. *Oncotarget, 7*, 52597-52612. ↗

Herbst, RS. (2004). Review of epidermal growth factor receptor biology. *Int J Radiat Oncol Biol Phys, 59*, 21-6. ↗

Dzul Keflee, R., Bignon, J., Leong, KH., Ogawa, S., Kong, KW., Chan, MC. (2022). Overview of the multifaceted resistances toward EGFR-TKIs and new chemotherapeutic strategies in non-small cell lung cancer. *Biochem Pharmacol, 205*, 115262. ↗

Wells, A. (1999). EGF receptor. *Int J Biochem Cell Biol, 31*, 637-43. ↗

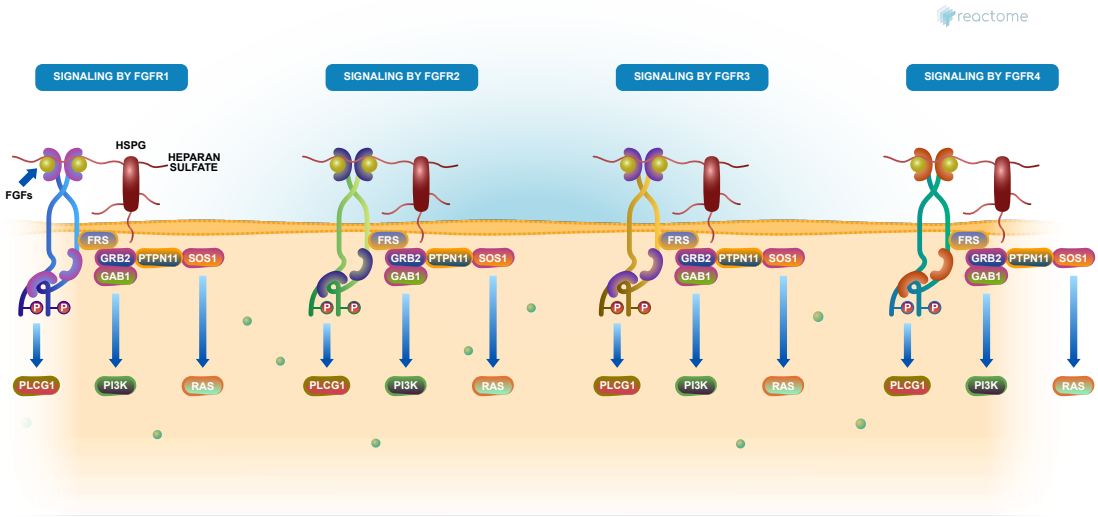
Editions

2008-02-28	Authored	Jassal, B., Castagnoli, L.
2008-02-28	Reviewed	Heldin, CH., Muthuswamy, S.
2011-08-25	Edited	Orlic-Milacic, M.
2023-11-08	Reviewed	Hill, DP.

Signaling by FGFR ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-190236



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

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

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

Literature references

Beenken, A., Mohammadi, M. (2009). The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov, 8*, 235-53. ↗

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

Schlessinger, J. (2004). Common and distinct elements in cellular signaling via EGF and FGF receptors. *Science, 306*, 1506-7. ↗

Ornitz, DM., Marie, PJ. (2002). FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. *Genes Dev, 16*, 1446-65. ↗

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

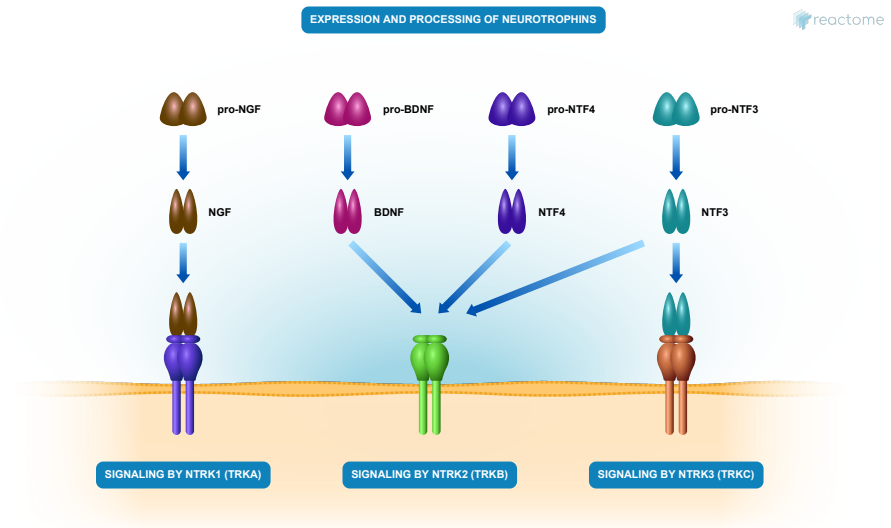
Editions

2007-01-10	Authored	de Bono, B.
2007-02-07	Reviewed	Mohammadi, M.
2007-02-11	Edited	de Bono, B., D'Eustachio, P.
2011-08-26	Reviewed	Gotoh, N.

Signaling by NTRKs ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-166520



Neurotrophins (NGF, BDNF, NTF3 and NTF4) play pivotal roles in survival, differentiation, and plasticity of neurons in the peripheral and central nervous system. They are produced, and secreted in minute amounts, by a variety of tissues. They signal through two types of receptors: NTRK (TRK) tyrosine kinase receptors (TRKA, TRKB, TRKC), which differ in their preferred neurotrophin ligand, and p75NTR death receptor, which interacts with all neurotrophins. Besides the nervous system, TRK receptors and p75NTR are expressed in a variety of other tissues. For review, please refer to Bibel and Barde 2000, Poo 2001, Lu et al. 2005, Skaper 2012, Park and Poo 2013.

NTRK receptors, NTRK1 (TRKA), NTRK2 (TRKB) and NTRK3 (TRKC) are receptor tyrosine kinases activated by ligand binding to their extracellular domain. Ligand binding induces receptor dimerization, followed by trans-autophosphorylation of dimerized receptors on conserved tyrosine residues in the cytoplasmic region. Phosphorylated tyrosines in the intracellular domain of the receptor serve as docking sites for adapter proteins, triggering downstream signaling cascades.

NTRK1 (TRKA) is the receptor for the nerve growth factor (NGF). NGF is primarily secreted by tissues that are innervated by sensory and sympathetic neurons. NTRK1 signaling promotes growth and survival of neurons during embryonic development and maintenance of neuronal cell integrity in adulthood (reviewed by Marlin and Li 2015).

Brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NTF4, also known as NT-4) are two high affinity ligands for NTRK2 (TRKB). Neurotrophin-3 (NTF3, also known as NT-3) binds to NTRK2 with low affinity and may not be a physiologically relevant ligand. Nerve growth factor (NGF), a high affinity ligand for NTRK1, does not interact with NTRK2. NTRK2 signaling is implicated in neuronal development in both the peripheral (PNS) and central nervous system (CNS) and may play a role in long-term potentiation (LTP) and learning (reviewed by Minichiello 2009). NTRK2 may modify neuronal excitability and synaptic transmission by directly phosphorylating voltage gated channels (Rogalski et al. 2000).

NTF3 (NT-3) is the ligand for NTRK3 (TRKC). Signaling downstream of activated NTRK3, regulates cell survival, proliferation and motility. In the absence of its ligand, NTRK3 functions as a dependence receptor and triggers BAX and CASP9-dependent cell death (Tauszig-Delamasure et al. 2007, Ichim et al. 2013).

Literature references

Cabrera, JR., Bouzas-Rodriguez, J., Bordeaux, MC., Tauszig-Delamasure, S., Mehlen, P., Yu, LY. et al. (2007). The TrkC receptor induces apoptosis when the dependence receptor notion meets the neurotrophin paradigm. *Proc. Natl. Acad. Sci. U.S.A., 104*, 13361-6. ↗

Poo, MM., Park, H. (2013). Neurotrophin regulation of neural circuit development and function. *Nat. Rev. Neurosci., 14*, 7-23.

Pang, PT., Woo, NH., Lu, B. (2005). The yin and yang of neurotrophin action. *Nat. Rev. Neurosci., 6*, 603-14.

Mehlen, P., Coelho-Aguiar, JM., Arumäe, U., Lefebvre, J., Tulasne, D., Le Douarin, N. et al. (2013). The dependence receptor TrkC triggers mitochondria-dependent apoptosis upon Cobra-1 recruitment. *Mol. Cell, 51*, 632-46.

Marlin, MC., Li, G. (2015). Biogenesis and function of the NGF/TrkA signaling endosome. *Int Rev Cell Mol Biol, 314*, 239-57.

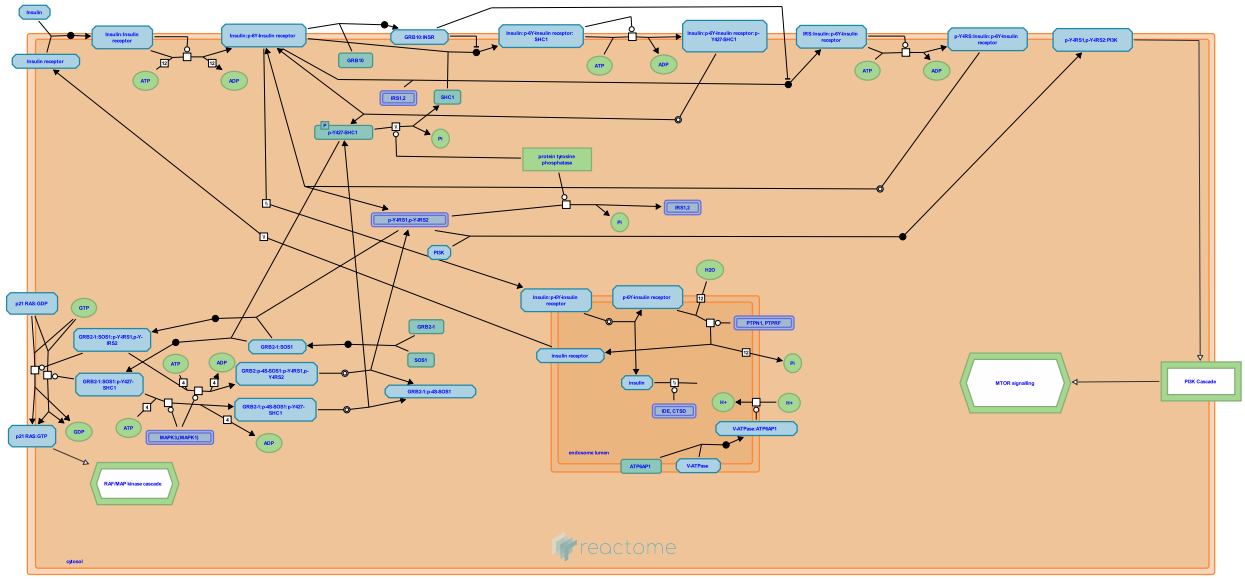
Editions

2006-10-10	Edited	Jassal, B.
2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

Signaling by Insulin receptor ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-74752



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

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

Literature references

White, MF., Kahn, CR. (1994). The insulin signaling system. *J Biol Chem, 269*, 1-4. ↗

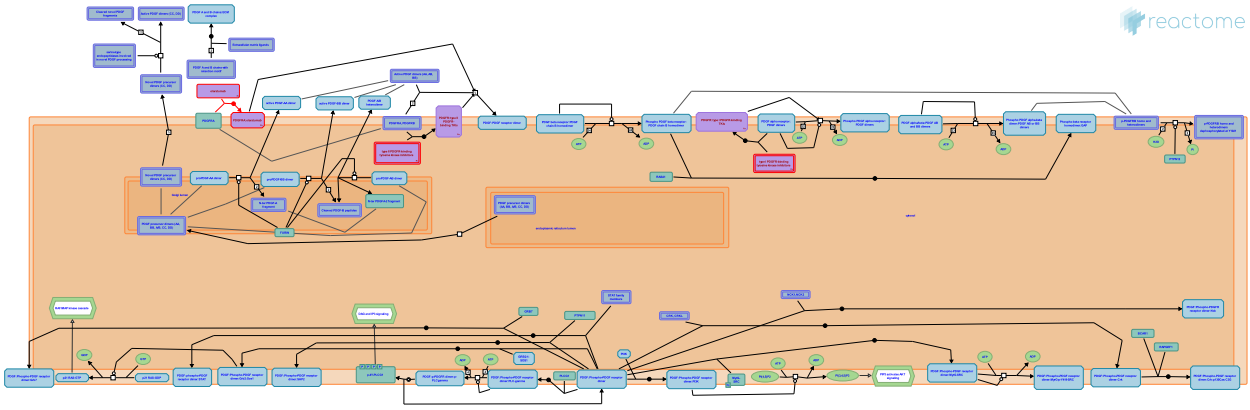
Editions

2003-07-31	Authored	Bevan, AP.
2024-03-06	Edited	Schmidt, EE.
2024-03-06	Reviewed	Barroso, I., Stanley, FM.

Signaling by PDGF ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-186797



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

Literature references

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

Ostman, A., Heldin, CH., Rönnstrand, L. (1998). Signal transduction via platelet-derived growth factor receptors. *Biochim Biophys Acta, 1378*, F79-113. ↗

Westermark, B., Heldin, CH. (1999). Mechanism of action and in vivo role of platelet-derived growth factor. *Physiol Rev, 79*, 1283-316. ↗

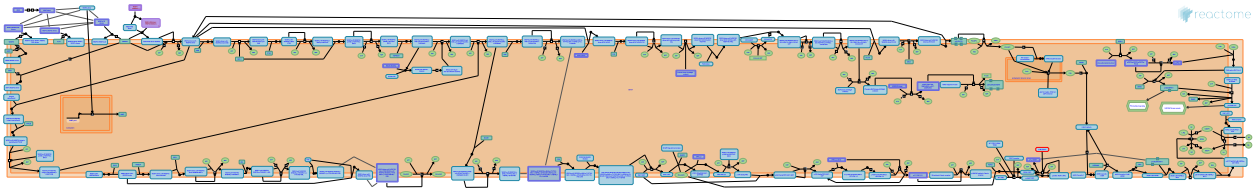
Editions

2008-11-24	Reviewed	Heldin, CH.
2008-11-24	Authored, Edited	Jassal, B., Garapati, P V.

Signaling by VEGF ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-194138



In normal development vascular endothelial growth factors (VEGFs) are crucial regulators of vascular development during embryogenesis (vasculogenesis) and blood-vessel formation in the adult (angiogenesis). In tumor progression, activation of VEGF pathways promotes tumor vascularization, facilitating tumor growth and metastasis. Abnormal VEGF function is also associated with inflammatory diseases including atherosclerosis, and hyperthyroidism. The members of the VEGF and VEGF-receptor protein families have distinct but overlapping ligand-receptor specificities, cell-type expression, and function. VEGF-receptor activation in turn regulates a network of signaling processes in the body that promote endothelial cell growth, migration and survival (Hicklin and Ellis, 2005; Shibuya and Claesson-Welsh, 2006).
Molecular features of the VGF signaling cascades are outlined in the figure below (from Olsson et al. 2006; Nature Publishing Group). Tyrosine residues in the intracellular domains of VEGF receptors 1, 2,and 3 are indicated by dark blue boxes; residues susceptible to phosphorylation are numbered. A circled R indicates that phosphorylation is regulated by cell state (VEGFR2), by ligand binding (VEGFR1), or by heterodimerization (VEGFR3). Specific phosphorylation sites (boxed numbers) bind signaling molecules (dark blue ovals), whose interaction with other cytosolic signaling molecules (light blue ovals) leads to specific cellular (pale blue boxes) and tissue-level (pink boxes) responses in vivo. Signaling cascades whose molecular details are unclear are indicated by dashed arrows. DAG, diacylglycerol; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; FAK, focal adhesion kinase; HPC, hematopoietic progenitor cell; HSP27, heat-shock protein-27; MAPK, mitogen-activated protein kinase; MEK, MAPK and ERK kinase; PI3K, phosphatidylinositol 3' kinase; PKC, protein kinase C; 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.

Literature references

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

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

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

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

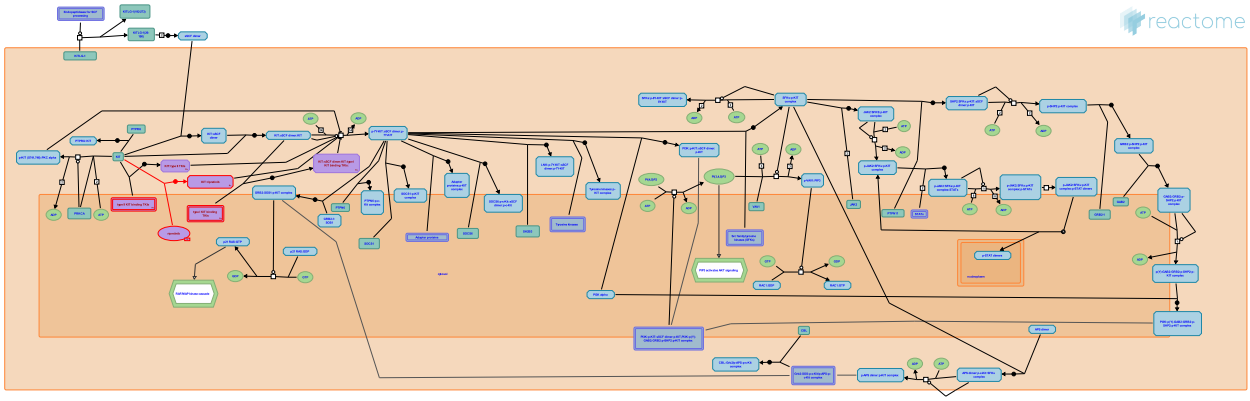
Editions

2008-02-28	Reviewed	Claesson-Welsh, L.
2013-08-30	Authored, Edited	Garapati, P V.

Signaling by SCF-KIT ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-1433557



Stem cell factor (SCF) is a growth factor with membrane bound and soluble forms. It is expressed by fibroblasts and endothelial cells throughout the body, promoting proliferation, migration, survival and differentiation of 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.

Literature references

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

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

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

Clark, SC., Ricciardi, ST., Crosier, PS., Vitas, MR., Hall, LR., Crosier, KE. (1993). Expression of isoforms of the human receptor tyrosine kinase c-kit in leukemic cell lines and acute myeloid leukemia. *Blood, 82*, 1151-8. ↗

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

Editions

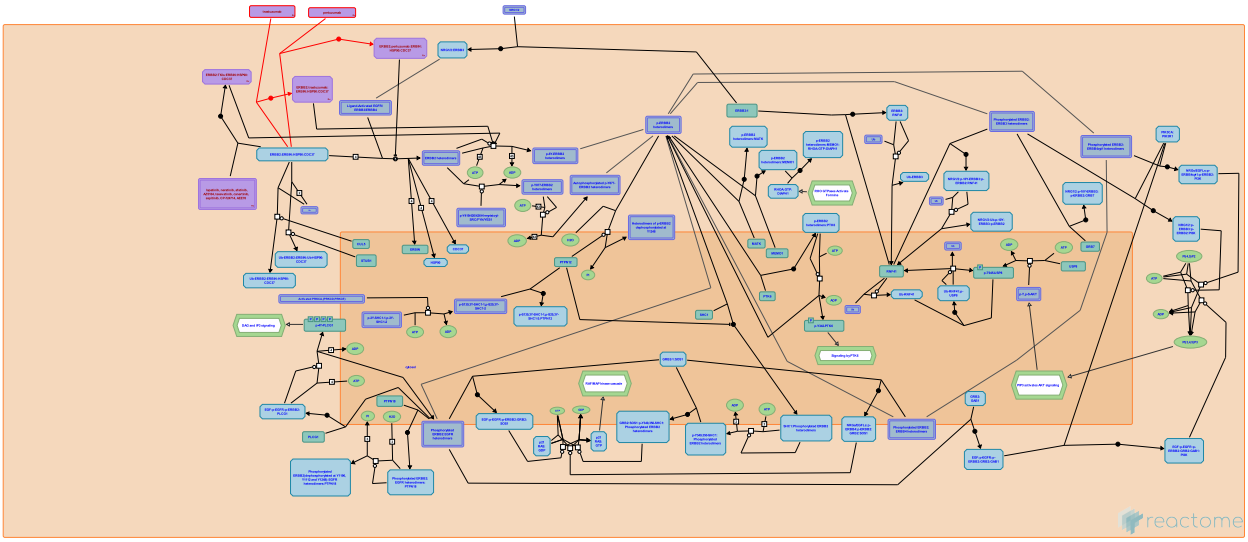
2011-07-11	Authored, Edited	Garapati, P V.
2011-08-22	Reviewed	Rönnstrand, L.

Signaling by ERBB2 ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-1227986

Compartments: cytosol, extracellular region, plasma membrane



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.

Editions

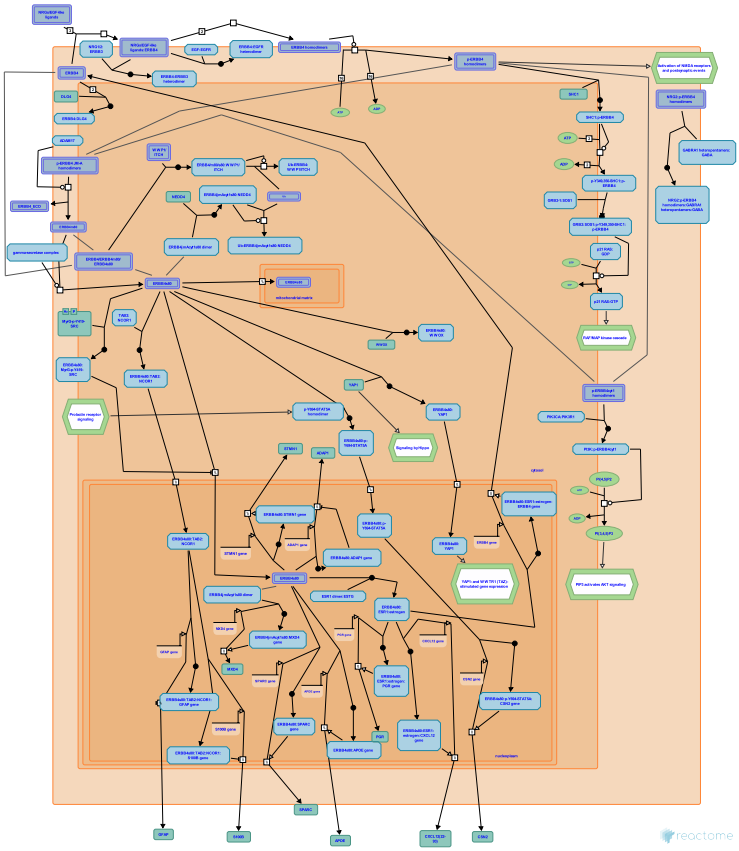
2011-11-04	Authored	Orlic-Milacic, M.
2011-11-07	Edited	D'Eustachio, P., Matthews, L.
2011-11-11	Reviewed	Neckers, LM., Xu, W.

Signaling by ERBB4 ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-1236394

Compartments: cytosol, extracellular region, plasma membrane



ERBB4, also known as HER4, belongs to the ERBB family of receptors, which also includes ERBB1 (EGFR/HER1), ERBB2 (HER2/NEU) and ERBB3 (HER3). Similar to EGFR, ERBB4 has an extracellular ligand binding domain, a single transmembrane domain and a cytoplasmic domain which contains an active tyrosine kinase and a C-tail with multiple phosphorylation sites. At least three and possibly four splicing isoforms of ERBB4 exist that differ in their C-tail and/or the extracellular juxtamembrane regions: ERBB4 JM-A CYT1, ERBB4 JM-A CYT2 and ERBB4 JM-B CYT1 (the existence of ERBB4 JM-B CYT2 has not been confirmed).

ERBB4 becomes activated by binding one of its seven ligands, three of which, HB-EGF, epiregulin EPR and betacellulin BTC, are EGF-like (Elenius et al. 1997, Riese et al. 1998), while four, NRG1, NRG2, NRG3 and NRG4, belong to the related neuregulin family (Tzahar et al. 1994, Carraway et al. 1997, Zhang et al. 1997, Hayes et al. 2007). Upon ligand binding, ERBB4 forms homodimers (Sweeney et al. 2000) or it heterodimerizes with ERBB2 (Li et al. 2007). Dimers of ERBB4 undergo trans-autophosphorylation on tyrosine residues in the C-tail (Cohen et al. 1996, Kaushansky et al. 2008, Hazan et al. 1990, Li et al. 2007), triggering downstream signaling cascades. The pathway Signaling by ERBB4 only shows signaling by ERBB4 homodimers. Signaling by heterodimers of ERBB4 and ERBB2 is shown in the pathway Signaling by ERBB2. Ligand-stimulated ERBB4 is also able to form heterodimers with ligand-stimulated EGFR (Cohen et al. 1996) and ligand-stimulated ERBB3 (Riese et al. 1995). Dimers of ERBB4 with EGFR and dimers of ERBB4 with ERBB3 were demonstrated in mouse cell lines in which human ERBB4 and EGFR or ERBB3 were exogenously expressed. These heterodimers undergo trans-autophosphorylation. The promiscuous heteromerization of ERBBs adds combinatorial diversity to ERBB signaling processes. As ERBB4 binds more ligands than other ERBBs, but has restricted expression, ERBB4 expression channels responses to ERBB ligands. The signaling capabilities of the four receptors have been compared (Schulze et al. 2005).

As for other receptor tyrosine kinases, ERBB4 signaling effectors are largely dictated through binding of effector proteins to ERBB4 peptides that are phosphorylated upon ligand binding. All splicing isoforms of ERBB4 possess two tyrosine residues in the C-tail that serve as docking sites for SHC1 (Kaushansky et al. 2008, Pinkas-Kramarski et al. 1996, Cohen et al. 1996). Once bound to ERBB4, SHC1 becomes phosphorylated on tyrosine residues by the tyrosine kinase activity of ERBB4, which enables it to recruit the complex of GRB2 and SOS1, resulting in the

guanyl-nucleotide exchange on RAS and activation of RAF and MAP kinase cascade (Kainulainen et al. 2000).

The CYT1 isoforms of ERBB4 also possess a C-tail tyrosine residue that, upon trans-autophosphorylation, serves as a docking site for the p85 alpha subunit of PI3K (Kaushansky et al. 2008, Cohen et al. 1996), leading to assembly of an active PI3K complex that converts PIP2 to PIP3 and activates AKT signaling (Kainulainen et al. 2000).

Besides signaling as a conventional transmembrane receptor kinase, ERBB4 differs from other ERBBs in that JM-A isoforms signal through efficient release of a soluble intracellular domain. Ligand activated homodimers of ERBB4 JM-A isoforms (ERBB4 JM-A CYT1 and ERBB4 JM-A CYT2) undergo proteolytic cleavage by ADAM17 (TACE) in the juxtamembrane region, resulting in shedding of the extracellular domain and formation of an 80 kDa membrane bound ERBB4 fragment known as ERBB4 m80 (Rio et al. 2000, Cheng et al. 2003). ERBB4 m80 undergoes further proteolytic cleavage, mediated by the gamma-secretase complex, which releases the soluble 80 kDa ERBB4 intracellular domain, known as ERBB4 s80 or E4ICD, into the cytosol (Ni et al. 2001). ERBB4 s80 is able to translocate to the nucleus, promote nuclear translocation of various transcription factors, and act as a transcription co-factor. For example, in mammary cells, ERBB4 binds SH2 transcription factor STAT5A. ERBB4 s80 shuttles STAT5A to the nucleus, and actsa as a STAT5A co-factor in binding to and promoting transcription from the beta-casein (CSN2) promoter, and may be involved in the regulation of other lactation-related genes (Jones et al. 1999, Williams et al. 2004, Muraoka-Cook et al. 2008). ERBB4 s80 binds activated estrogen receptor in the nucleus and acts as a transcriptional co-factor in promoting transcription of some estrogen-regulated genes, including progesterone receptor gene NR3C3 and CXCL12 (SDF1) (Zhu et al. 2006). In neuronal precursors, ERBB4 s80 binds the complex of TAB and NCOR1, helps to move the complex into the nucleus, and is a co-factor of TAB:NCOR1-mediated inhibition of expression of astrocyte differentiation genes GFAP and S100B (Sardi et al. 2006).

The C-tail of ERBB4 possesses several WW-domain binding motifs (three in CYT1 isoform and two in CYT2 isoform), which enable interaction of ERBB4 with WW-domain containing proteins. ERBB4 s80, through WW-domain binding motifs, interacts with YAP1 transcription factor, a known proto-oncogene, and is a co-regulator of YAP1-mediated transcription in association with TEAD transcription factors (Komuro et al. 2003, Omerovic et al. 2004). Hence, the WW binding motif couples ERBB4 to the major effector arm of the HIPPO signaling pathway. The tumor suppressor WWOX, another WW-domain containing protein, competes with YAP1 in binding to ERBB4 s80 and prevents translocation of ERBB4 s80 to the nucleus (Aqeilan et al. 2005).

WW-domain binding motifs in the C-tail of ERBB4 play an important role in the downregulation of ERBB4 receptor signaling, enabling the interaction of intact ERBB4, ERBB4 m80 and ERBB4 s80 with NEDD4 family of E3 ubiquitin ligases WWP1 and ITCH. The interaction of WWP1 and ITCH with intact ERBB4 is independent of receptor activation and autophosphorylation. Binding of WWP1 and ITCH ubiquitin ligases leads to ubiquitination of ERBB4 and its cleavage products, and subsequent degradation through both proteasomal and lysosomal routes (Omerovic et al. 2007, Feng et al. 2009). In addition, the s80 cleavage product of ERBB4 JM-A CYT-1 isoform is the target of NEDD4 ubiquitin ligase. NEDD4 binds ERBB4 JM-A CYT-1 s80 (ERBB4jmAcyt1s80) through its PIK3R1 interaction site and mediates ERBB4jmAcyt1s80 ubiquitination, thereby decreasing the amount of ERBB4jmAcyt1s80 that reaches the nucleus (Zeng et al. 2009).

ERBB4 also binds the E3 ubiquitin ligase MDM2, and inhibitor of p53 (Arasada et al. 2005). Other proteins that bind to ERBB4 intracellular domain have been identified by co-immunoprecipitation and mass spectrometry (Gilmore-Hebert et al., 2010), and include transcriptional co-repressor TRIM28/KAP1, which promotes chromatin compaction. DNA damage signaling through ATM releases TRIM28-associated heterochromatinization. Interactions of ERBB4 with TRIM28 and MDM2 may be important for integration of growth factor responses and DNA damage responses.

In human breast cancer cell lines, ERBB4 activation enhances anchorage-independent colony formation in soft agar but inhibits cell growth in a monolayer culture. Different ERBB4 ligands induce different gene expression changes in breast cancer cell lines. Some of the genes induced in response to ERBB4 signaling in breast cancer cell lines are RAB2, EPS15R and GATA4. It is not known if these gene are direct transcriptional targets of ERBB4 (Amin et al. 2004).

Transcriptome and ChIP-seq comparisons of full-length and intracellular domain isoforms in isogenic MCF10A mammary cell background have revealed the diversification of ERBB4 signaling engendered by alternative splicing and cleavage (Wali et al., 2014). ERBB4 broadly affected protease expression, cholesterol biosynthesis, HIF1-alpha signaling, and HIPPO signaling pathways, and other pathways were differentially activated by CYT1 and CYT2 isoforms. For example, CYT1 promoted expression of transcription factors TWIST1 and SNAIL1 that promote epithelial-mesenchymal transition. HIF1-alpha and HIPPO signaling are mediated, respectively, by binding of ERBB4 to HIF1-alpha and to YAP (Paatero et al., 2012, Komuro et al., 2003). ERBB4 increases activity of the transcription factor SREBF2, resulting in increased expression of SREBF2-target genes involved in cholesterol biosynthesis. The mechanism is not known and may involve facilitation of SREBF2 cleavage through ERBB4-

mediated PI3K signaling (Haskins et al. 2016).

In some contexts, ERBB4 promotes growth suppression or apoptosis (Penington et al., 2002). Activation of ERBB4 in breast cancer cell lines leads to JNK dependent increase in BRCA1 mRNA level and mitotic cell cycle delay, but the exact mechanism has not been elucidated (Muraoka Cook et al. 2006). The nature of growth responses may be connected with the spliced isoforms expressed. In comparisons of CYT1 vs CYT2 (full-length and ICD) expression in mammary cells, CYT1 was a weaker growth inducer, associated with attenuated MAPK signaling relative to CYT2 (Wali et al., 2014). ERBB4 s80 is also able to translocate to the mitochondrial matrix, presumably when its nuclear translocation is inhibited. Once in the mitochondrion, the BH3 domain of ERBB4, characteristic of BCL2 family members, may enable it to act as a pro apoptotic factor (Naresh et al. 2006).

ERBB4 plays important roles in the developing and adult nervous system. Erbb4 deficiency in somatostatin-expressing neurons of the thalamic reticular nucleus alters behaviors dependent on sensory selection (Ahrens et al. 2015). NRG1-activated ERBB4 signaling enhances AMPA receptor responses through PKC-dependent AMPA receptor exocytosis. This results in an increased excitatory input to parvalbumin-expressing inhibitory neurons in the visual cortex and regulates visual cortical plasticity (Sun et al. 2016). NRG1-activated ERBB4 signaling is involved in GABAergic activity in amygdala which mediates fear conditioning (fear memory) (Lu et al. 2014). Conditional Erbb4 deletion from fast-spiking interneurons, chandelier and basket cells of the cerebral cortex leads to synaptic defects associated with increased locomotor activity and abnormal emotional, social and cognitive function that can be linked to some of the schizophrenia features. The level of GAD1 (GAD67) protein is reduced in the cortex of conditional Erbb4 mutants. GAD1 is a GABA synthesizing enzyme. Cortical mRNA levels of GAD67 are consistently decreased in schizophrenia (Del Pino et al. 2014). Erbb4 is expressed in the GABAergic neurons of the bed nucleus stria terminalis, a part of the extended amygdala. Inhibition of NRG1-triggered ERBB4 signaling induces anxiety-like behavior, which depends on GABAergic neurotransmission. NRG1-ERBB4 signaling stimulates presynaptic GABA release, but the exact mechanism is not known (Geng et al. 2016). NRG1 protects cortical interneurons against ischemic brain injury through ERBB4-mediated increase in GABAergic transmission (Guan et al. 2015). NRG2-activated ERBB4 can reduce the duration of GABAergic transmission by binding to GABA receptors at the postsynaptic membrane via their GABRA1 subunit and promoting endocytosis of GABA receptors (Mitchell et al. 2013). NRG1 promotes synchronization of prefrontal cortex interneurons in an ERBB4 dependent manner (Hou et al. 2014). NRG1-ERBB4 signaling protects neurons from the cell death induced by a mutant form of the amyloid precursor protein (APP) (Woo et al. 2012).

Clinical relevance of ERBB4 has been identified in several contexts. In cancer, putative and validated gain-of-function mutations or gene amplification that may be drivers have been identified at modest frequencies, and may also contribute to resistance to EGFR and ERBB2-targeted therapies. This is noteworthy as ERBB4 kinase activity is inhibited by pan-ERBB tyrosine kinase inhibitors, including lapatinib, which is approved by the US FDA. The reduced prevalence relative to EGFR and ERBB2 in cancer may reflect more restricted expression of ERBB4, or differential signaling, as specific ERBB4 isoforms have been linked to growth inhibition or apoptosis in experimental systems. ERBB2/ERBB4 heterodimers protect cardiomyocytes, so reduced activity of ERBB4 in patients treated with the ERBB2-targeted therapeutic antibody trastuzumab may contribute to the cardiotoxicity of this agent when used in combination with (cardiotoxic) anthracyclines.

With the importance of ERBB4 in developing and adult nervous system, NRG1 and/or ERBB4 polymorphisms, splicing aberrations and mutations have been linked to nervous system disorders including schizophrenia and amyotrophic lateral sclerosis, although these findings are not yet definitive.

Literature references

Carraway KL, 3rd., Riese DJ, 2nd., Cantley, LC., Diamonti, AJ., Lai, C., Sweeney, C. (2000). Ligand discrimination in signaling through an ErbB4 receptor homodimer. *J Biol Chem, 275*, 19803-7. ↗

Earp HS, 3rd., Muraoka-Cook, RS., Hunter, D., Caskey, LS., Sandahl, MA., Atfi, A. et al. (2009). The E3 ubiquitin ligase WWP1 selectively targets HER4 and its proteolytically derived signaling isoforms for degradation. *Mol Cell Biol, 29*, 892-906. ↗

Navin, NE., Sudol, M., Komuro, A., Nagai, M. (2003). WW domain-containing protein YAP associates with ErbB-4 and acts as a co-transcriptional activator for the carboxyl-terminal fragment of ErbB-4 that translocates to the nucleus. *J Biol Chem, 278*, 33334-41. ↗

Fraioli, R., Frati, L., Puggioni, EM., Gulino, A., Alimandi, M., Omerovic, J. et al. (2004). Ligand-regulated association of ErbB-4 to the transcriptional co-activator YAP65 controls transcription at the nuclear level. *Exp Cell Res, 294*, 469-79. ↗

Ghosh, S., Ahrens, S., Hwang, GR., Yu, K., Li, B., He, M. et al. (2015). ErbB4 regulation of a thalamic reticular nucleus circuit for sensory selection. *Nat. Neurosci., 18*, 104-11. ↗

Editions

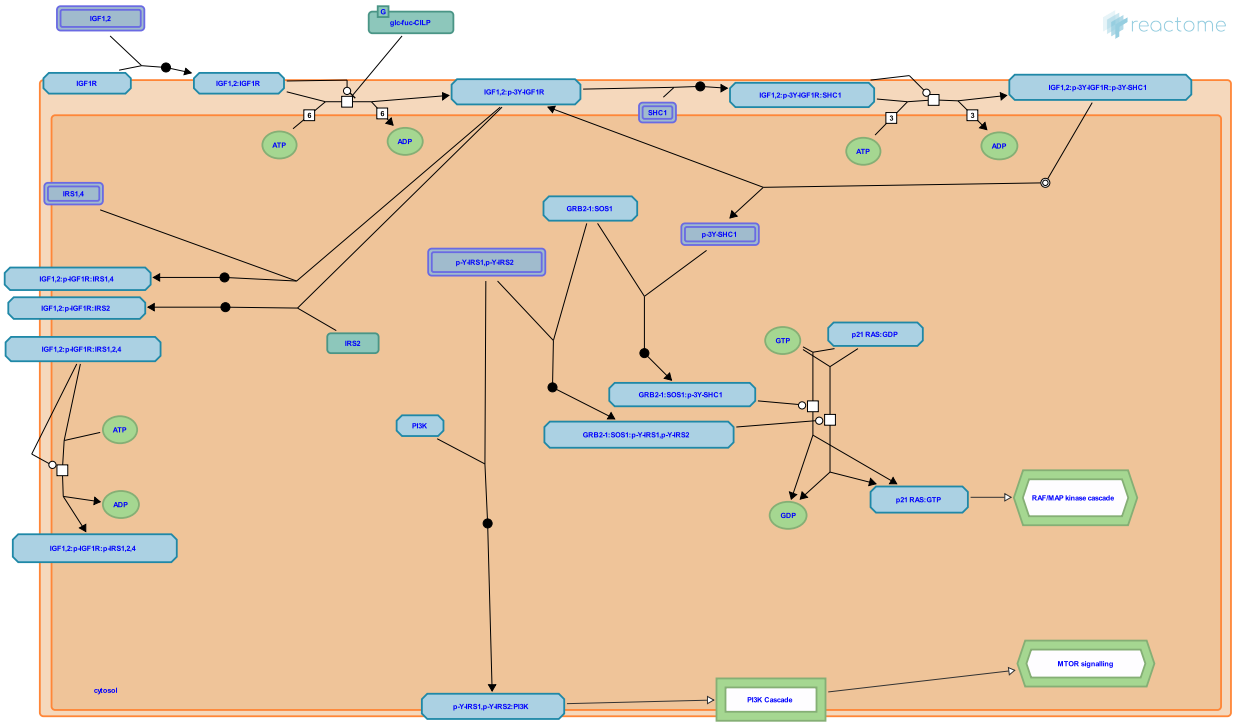
2011-11-04	Authored	Orlic-Milacic, M.
2011-11-07	Edited	D'Eustachio, P., Matthews, L.
2011-11-11	Reviewed	Harris, RC., Zeng, F.
2012-02-20	Reviewed	Earp HS, 3rd., Misior, AM.
2018-06-28	Revised	Orlic-Milacic, M.
2019-02-21	Authored, Revised	Stern, DF.
2019-03-06	Edited	Orlic-Milacic, M.

Signaling by Type 1 Insulin-like Growth Factor 1 Receptor (IGF1R) ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-2404192

Compartments: plasma membrane, extracellular region, cytosol



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).

Literature references

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

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

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

Holzenberger, M. (2011). Igf-I signaling and effects on longevity. *Nestle Nutr Workshop Ser Pediatr Program, 68*, 237-45; discussion 246-9. ↗

Knezević, J., Matijević, T., Pavelić, J. (2007). Biological & physiological aspects of action of insulin-like growth factor peptide family. *Indian J. Med. Res., 125*, 511-22. ↗

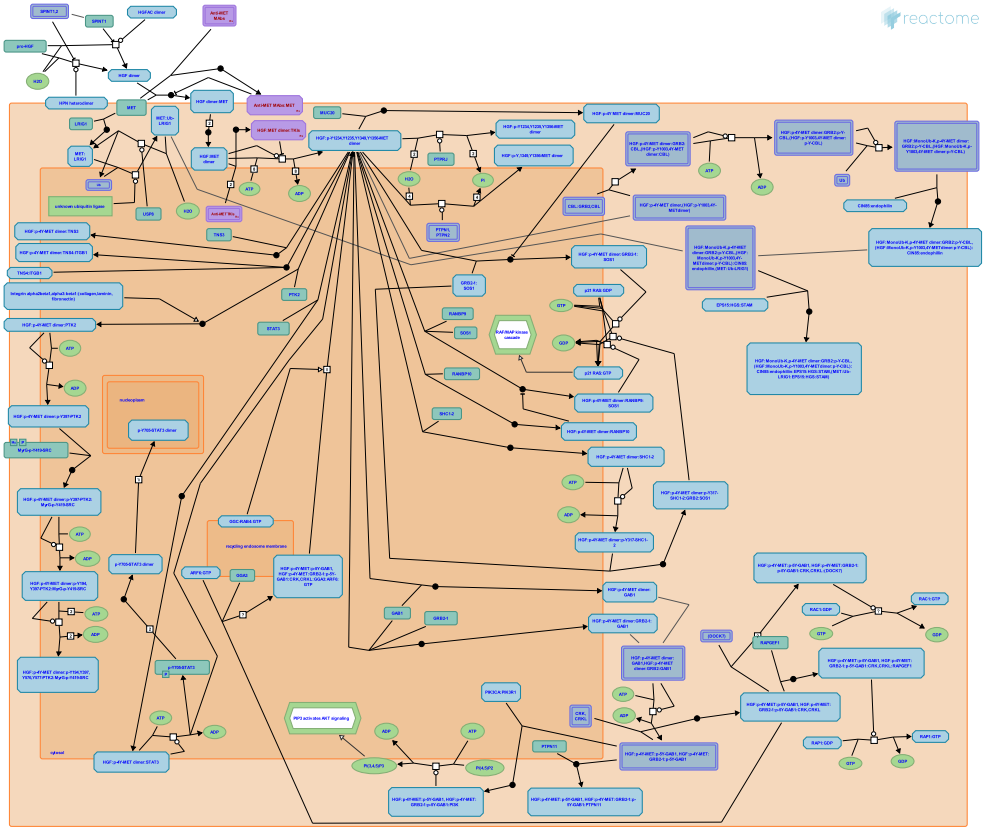
Editions

2012-07-08	Authored, Edited	May, B.
2012-11-10	Reviewed	Holzenberger, M.

Signaling by MET ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-6806834



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.

Literature references

Vande Woude, GF., Gherardi, E., Birchmeier, W., Birchmeier, C. (2003). Met, metastasis, motility and more. *Nat. Rev. Mol. Cell Biol., 4*, 915-25.

Gastaldi, S., Bertotti, A., Comoglio, PM., Rolland-Valognes, G., Hickman, JA., Torti, D. et al. (2009). Only a subset of Met-activated pathways are required to sustain oncogene addiction. *Sci Signal, 2*, ra80.

Chan, AM., Kmiecik, TE., Aaronson, SA., Rubin, JS., Vande Woude, GF., Faletto, DL. et al. (1991). Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. *Science, 251*, 802-4.

Vande Woude, G., Gherardi, E., Birchmeier, W., Birchmeier, C. (2012). Targeting MET in cancer: rationale and progress. *Nat. Rev. Cancer, 12*, 89-103.

Huebner, K., Croce, CM., Park, M., Blair, DG., Vande Woude, GF., Cooper, CS. et al. (1984). Molecular cloning of a new transforming gene from a chemically transformed human cell line. *Nature, 311*, 29-33.

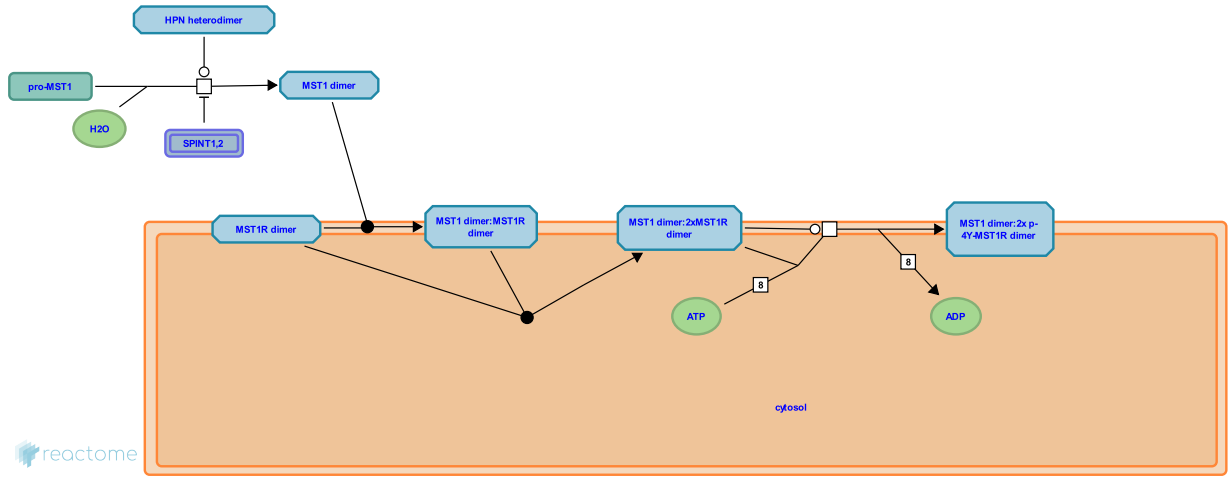
Editions

2016-06-14	Authored, Edited	Orlic-Milacic, M.
2016-07-11	Reviewed	Birchmeier, W., Heynen, G.

Signaling by MST1 ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-8852405



Inflammatory mediators such as growth factors produced by macrophages play an important role in the inflammatory response occurring during bacterial infection, tissue injury and immune responses. Many growth factors and their receptor-type protein tyrosine kinases (RTKs) play a critical role in inflammation, wound healing and tissue remodelling. The growth factor hepatocyte growth factor-like protein (MST1, also known as macrophage-stimulating protein, MSP) binds to a specific receptor, macrophage-stimulating protein receptor (MST1R, also known as RON, recepteur d'origine nantais). MST1 belongs to the kringle protein family, which includes HGF and plasminogen. It is produced by the liver and circulates in the blood as a biologically-inactive single chain precursor (pro-MST1). Proteolytic cleavage of pro-MST1 into the biologically-active MST1 dimer is necessary for receptor binding. Cleavage occurs during blood coagulation and at inflammatory sites, the resultant MST1 dimer then binds MST1R receptors on local macrophages. MST1R is ubiquitously expressed but mainly in epithelial cells.

MST1 binding to MST1R promotes receptor homodimerisation which in turn allows autophosphorylation of two tyrosine residues within the catalytic site which regulates kinase activity and allows phosphorylation of the carboxy-terminal binding site of the receptor. The docking site is essential for downstream signaling through direct and indirect binding of SH2 domain-containing adaptor proteins such as GRB2, PI3K, and SRC. MST1/MST1R signaling plays a dual role in regulating inflammation; initially stimulating chemotaxis and phagocytosis (macrophage activation) and then exerts broad inhibitory effects on macrophages, limiting the extent of inflammtory responses (Wang et al. 2002). MST1R is upregulated in many epithelial cancers where it is thought to play a role in the progression of these types of cancer (Kretschmann et al. 2010).

Literature references

Chen, YQ., Wang, MH., Zhou, YQ. (2002). Macrophage-stimulating protein and RON receptor tyrosine kinase: potential regulators of macrophage inflammatory activities. *Scand. J. Immunol., 56*, 545-53. ↗

Kretschmann, KL., Buys, SS., Eyob, H., Welm, AL. (2010). The macrophage stimulating protein/Ron pathway as a potential therapeutic target to impede multiple mechanisms involved in breast cancer progression. *Curr Drug Targets, 11*, 1157-68. ↗

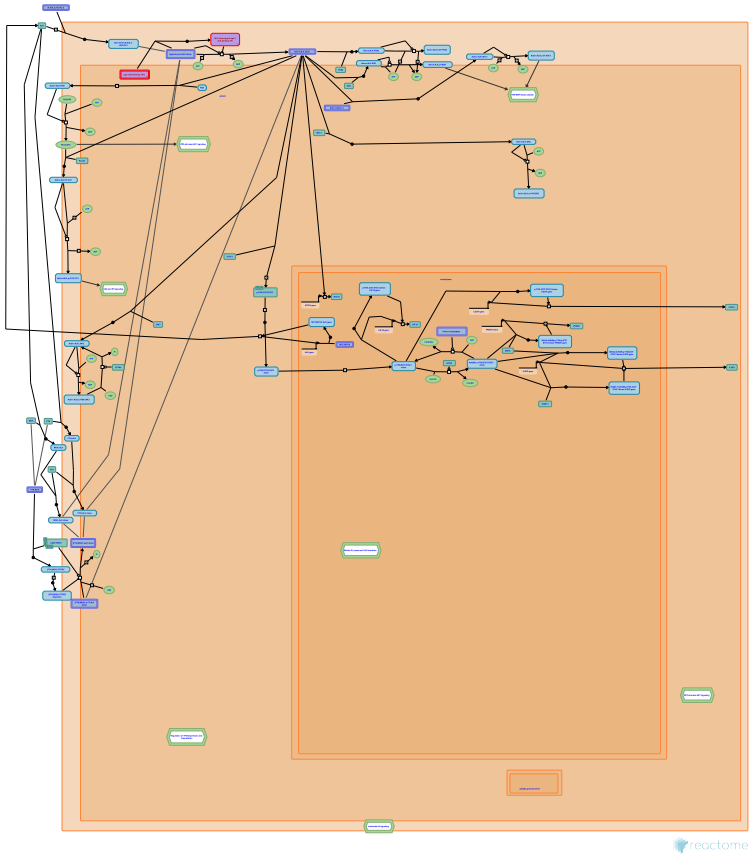
Editions

2016-01-11	Reviewed	D'Eustachio, P.
2016-01-18	Authored, Edited	Jassal, B.

Signaling by ALK ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-201556



The anaplastic lymphoma kinase (ALK) is a transmembrane receptor tyrosine kinase that, along with related receptor LTK (leukocyte tyrosine kinase receptor) is a member of the insulin receptor superfamily (Iwahara et al, 1997). ALK was discovered as an oncogene in anaplastic large cell lymphomas (ALCLs), but also plays an oncogenic role in other cancer types, such as non-small-cell lung cancer (NSCLC), inflammatory myofibroblastic tumours (IMT), melanoma, neuroblastoma and glioblastoma. In cancer, the chromosomal region encoding ALK frequently undergoes genomic rearrangements, resulting in the formation of ALK fusion proteins, such as NPM-ALK (the result of a translocation event, t(2;5)(p23;q35) which is predominant in ALCL) and EML4-ALK (an inversion event on chromosome 2) (Morris et al, 1994; Couts et al, 2018). These fusion proteins consist of the C-terminal region of ALK, encompassing the kinase domain and the effector protein binding domain (with loss of the transmembrane domain), while the N-terminus of the fusion protein contains the dimerization domain of the partner gene. Fusion proteins of ALK are therefore capable of ligand-independent dimerization, resulting in constitutive ALK signaling (reviewed in Duyster et al, 2001; Chiarle et al, 2008; Della Corte et al, 2018; Hallberg and Palmer, 2013; Hallberg and Palmer, 2016; Janoueix-Larousey et al, 2018; Ducray et al, 2019). Additionally, amplification of ALK and/or point mutations leading to its constitutive activation have been detected in neuroblastoma (reviewed in McDuff et al, 2011).

Many of the functional studies on ALK have been conducted in the context of oncogenic forms of the protein. In contrast, fewer studies have been conducted on the wild type protein under normal physiological conditions, and indeed, ALK was initially classed as an orphan receptor with no identified ligand. Two small heparin-binding growth factors, pleiotrophin (PTN) and midkine (MDK), were initially identified as potential ligands however subsequent studies failed to support this (Stoica et al, 2001; Stoica et al, 2002; Mathivet et al, 2007; Moog-Lutz et al, 2005; Motegi et al, 2004; reviewed in Wellstein et al, 2012; Winkler et al, 2014; Herradon and Perez-Garcia, 2014). More recently, ALKAL1 and ALKAL2 (also known as FAM150A and FAM150B) have been identified as ligands for both ALK and the related LTK receptor, albeit with differing potencies (Zhang et al, 2014; Guan et al, 2015; Reshetnyak et al, 2015; Reshetnyak et al, 2018; Fadeev et al, 2018; Reshetnyak et al, 2021; De Munck et al, 2021; Borenas et al, 2021; reviewed in Hallberg and Palmer, 2016). Whereas LTK receptor is potently activated by both ALKAL1 and ALKAL2, ALK is only weakly stimulated by ALKAL1 (Reshetnyak et al, 2015; Reshetnyak et al, 2018). Ligand

binding induces the dimerization of the receptor and transautophosphorylation, resulting in a fully activated receptor that triggers downstream signaling cascades such as RAS, PI3K and IRS1 signaling. ALK may also undergo ligand-independent activation through RPTPB/RPTPZ (Deuel et al, 2013).

ALK is mainly expressed in the developing central and peripheral nervous system and plays a role in differentiation during development (Souttou et al, 2001; Gouzi et al, 2005; Degoutin et al, 2007). In Drosophila and mice, ALK is a thinness gene involved in the resistance to weight gain (Orthofer et al, 2020). Through activation of STAT3 targets, ALK also appears to play a role in response to ethanol (Hamada et al, 2021).

Literature references

Kotani, M., Motegi, A., Sakuraba, H., Fujimoto, J., Yamamoto, T. (2004). ALK receptor tyrosine kinase promotes cell growth and neurite outgrowth. *J. Cell. Sci., 117*, 3319-29. ↗

Lai, WY., Mendoza-Garcia, P., Koster, J., Gaarder, J., Masudi, T., El Wakil, A. et al. (2021). ALK ligand ALKAL2 potentiates MYCN-driven neuroblastoma in the absence of ALK mutation. *EMBO J, 40*, e105784. ↗

Mendoza, P., Pfeifer, K., Mohammed, A., Wolfstetter, G., Palmer, RH., Halenbeck, R. et al. (2015). FAM150A and FAM150B are activating ligands for anaplastic lymphoma kinase. *Elife, 4*, e09811. ↗

Hallberg, B., Palmer, RH. (2016). The role of the ALK receptor in cancer biology. *Ann Oncol, 27*, iii4-iii15. ↗

Carvalho, NB., Raulais, D., Vigny, M., Souttou, B. (2001). Activation of anaplastic lymphoma kinase receptor tyrosine kinase induces neuronal differentiation through the mitogen-activated protein kinase pathway. *J. Biol. Chem., 276*, 9526-31. ↗

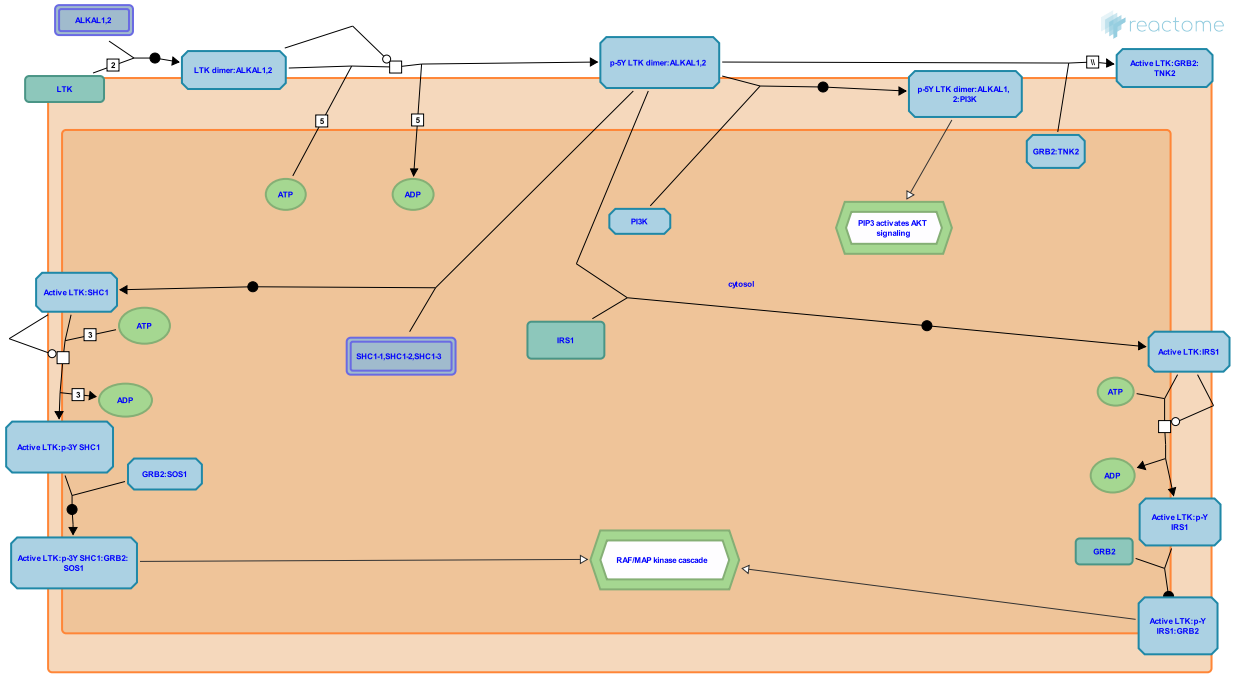
Editions

2007-08-21	Authored, Edited	Jassal, B.
2021-05-04	Reviewed	Inghirami, G.
2023-11-08	Reviewed	Turner, S.

Signaling by LTK ↗

Location: Signaling by Receptor Tyrosine Kinases

Stable identifier: R-HSA-9842663



Leukocyte tyrosine kinase (LTK) is a transmembrane receptor tyrosine kinase that is a member of the insulin growth factor receptor superfamily. LTK is most closely related to the ALK receptor, and may have originated as a result of a duplication event of the ALK gene (Krowelski and Dalla-Favera, 1991; Dornburg et al, 2021). The extracellular domains of ALK and LTK are characterized by a membrane proximal EGF-like (EGFL) module, a unique 250 amino acid glycine rich (GR) domain that, in Drosophila, is essential for function (Englund et al, 2003), as well as a TNF-like (TNFL) module. The ALK ECD additionally contains two MAM domains, an LDLa domain and a heparin-binding domain (HBD) that are not present in the LTK receptor (Iwahara et al, 1997; Morris et al, 1997; DeMunck et al, 2021). These differences in ECD may contribute to differences in the ligand binding affinities of the two receptors.
LTK is activated by the binding of cytokines ALKAL1 and ALKAL2 to the ECD (Zhang et al, 2014; Reshetnyak et al, 2015; Reshetnyak et al, 2018). Ligand binding induces trans-autophosphorylation in the intracellular domain of the receptor and promotes the interaction and activation of downstream signaling molecules such as SHC, IRS1, CBL and PI3K with the phosphorylated receptor (Kozutsumi et al, 1994; Honda et al, 1994; Ueno et al, 1995; Ueno et al, 1996; Ueno et al, 1997; Li et al, 2004; Yamada et al, 2008). Note however that much of the early functional studies on LTK were conducted before the identification of ALKAL1 and 2 as physiological ligands. In consequence, many of these studies were carried out using chimeric receptors consisting of the ECD (and stimulating ligands) of well-characterized receptors fused to the intracellular domain of LTK.
The exact role of LTK signaling is likewise not fully elucidated. Expression of the chimeric LTK proteins described above promotes neurite outgrowth and cell survival (Ueno et al, 1997; Yamada et al, 2008). A role for LTK in the regulation of transport from the ER to the Golgi has also been proposed, and one study suggests that LTK may actually bean ER-resident protein (Farhan et al, 2010; Centonze et al, 2019). More recently, fusions of LTK have been identified in non-small cell lung cancer (Izumi et al, 2021).

Literature references

Yazaki, Y., Mitani, K., Miyagawa, K., Kozutsumi, H., Hirai, H., Sasaki, K. et al. (1996). Growth and survival signals transmitted via two distinct NPXY motifs within leukocyte tyrosine kinase, an insulin receptor-related tyrosine kinase. *J Biol Chem, 271*, 27707-14. ↗

Yazaki, Y., Hirano, N., Kozutsumi, H., Tanaka, T., Hirai, H., Sasaki, K. et al. (1995). An epidermal growth factor receptor-leukocyte tyrosine kinase chimeric receptor generates ligand-dependent growth signals through the Ras signaling pathway. *J Biol Chem, 270*, 20135-42. ↗

Yazaki, Y., Toyoshima, H., Kozutsumi, H., Hirai, H., Hagiwara, K. (1994). Human ltk receptor tyrosine kinase binds to PLC-gamma 1, PI3-K, GAP and Raf-1 in vivo. *Oncogene, 9*, 2991-8. ↗

Yazaki, Y., Terasaki, F., Harada, K., Honda, H., Kawamura, K., Komuro, I. et al. (1999). Heart-specific activation of LTK results in cardiac hypertrophy, cardiomyocyte degeneration and gene reprogramming in transgenic mice. *Oncogene, 18*, 3821-30. ↗

Jiang, Y., Shirai, T., Matsuoka, S., Li, N., Tsurui, H., Koike, T. et al. (2004). Gain-of-function polymorphism in mouse and human Ltk: implications for the pathogenesis of systemic lupus erythematosus. *Hum Mol Genet, 13*, 171-9. ↗

Editions

2023-10-14	Authored, Edited	Rothfels, K.

Table of Contents