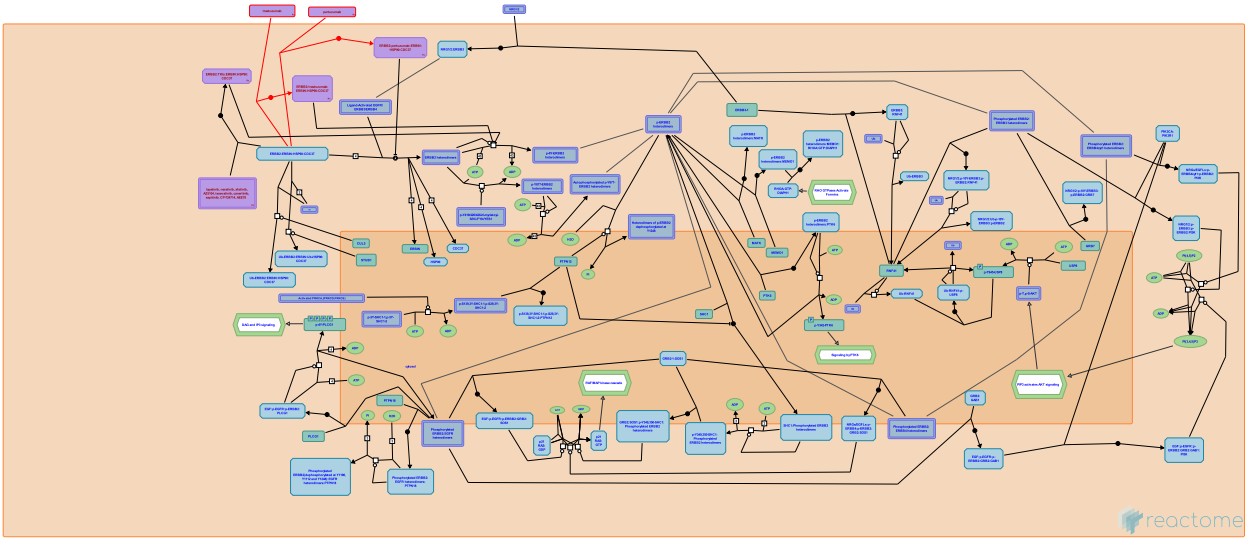
Signaling by ERBB2



Badache, A., D'Eustachio, P., Kancha, RK., Matthews, L., Neckers, LM., Orlic-Milacic, M., Pires, IM., Xu, W.

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

24/06/2024

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.
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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. ↗

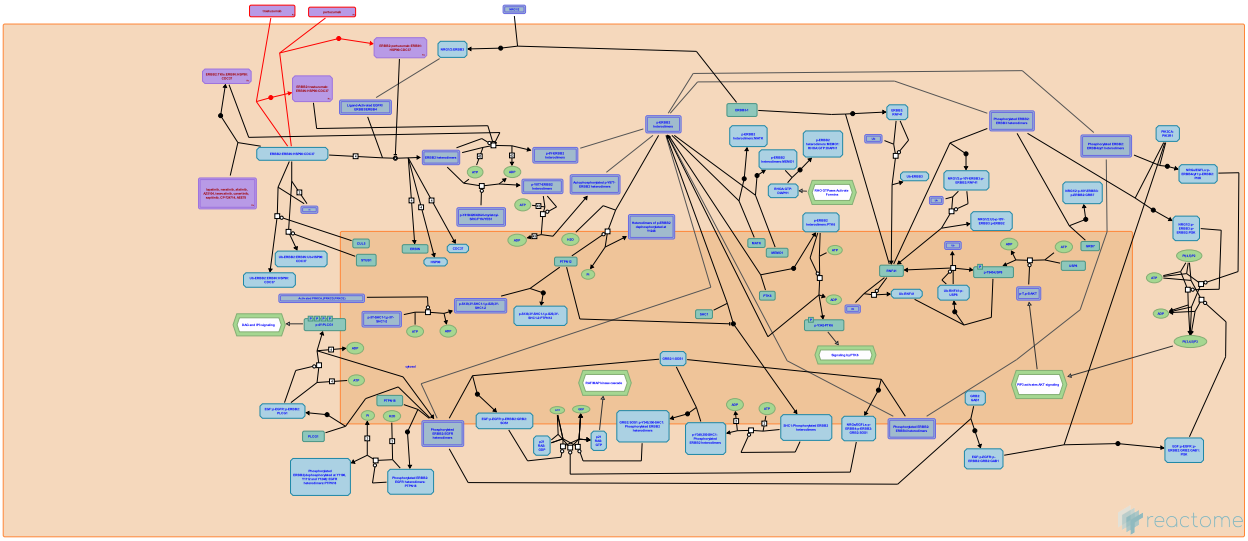
Reactome database release: 89

This document contains 10 pathways and 5 reactions (see Table of Contents)

Signaling by ERBB2 ↗

Stable identifier: R-HSA-1227986

Compartments: cytosol, plasma membrane, extracellular region



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

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

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

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

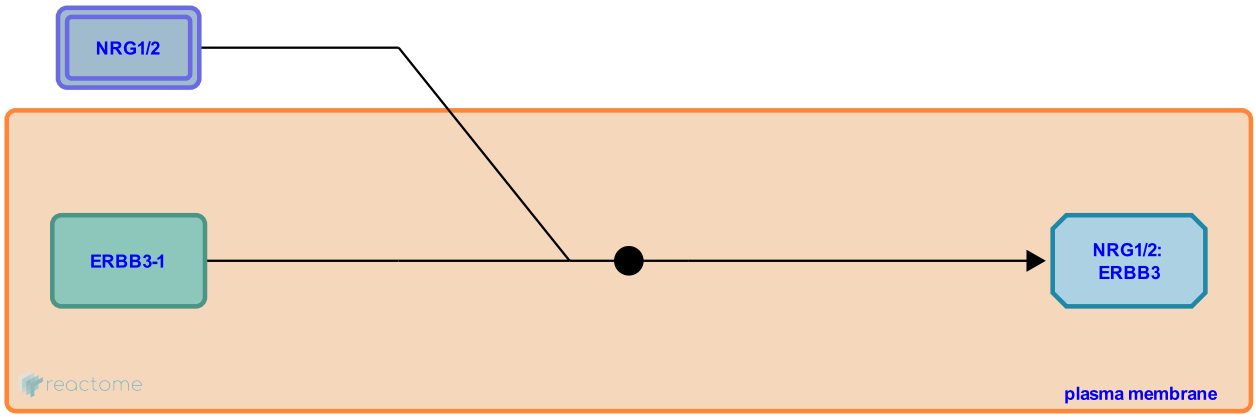
ERBB3 binds neuregulins ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1247497

Type: binding

Compartments: plasma membrane, extracellular region



ERBB3 becomes activated by binding either neuregulin 1 (NRG1) or neuregulin 2 (NRG2).

Followed by: ERBB2 forms heterodimers with ligand-activated ERBB receptors: EGFR, ERBB3 and ERBB4

Literature references

Chang, D., Levkowitz, G., Liu, N., Karunagaran, D., Yi, L., Yayon, A. et al. (1994). ErbB-3 and ErbB-4 function as the respective low and high affinity receptors of all Neu differentiation factor/heregulin isoforms. *J Biol Chem, 269*, 25226-33. ↗

Editions

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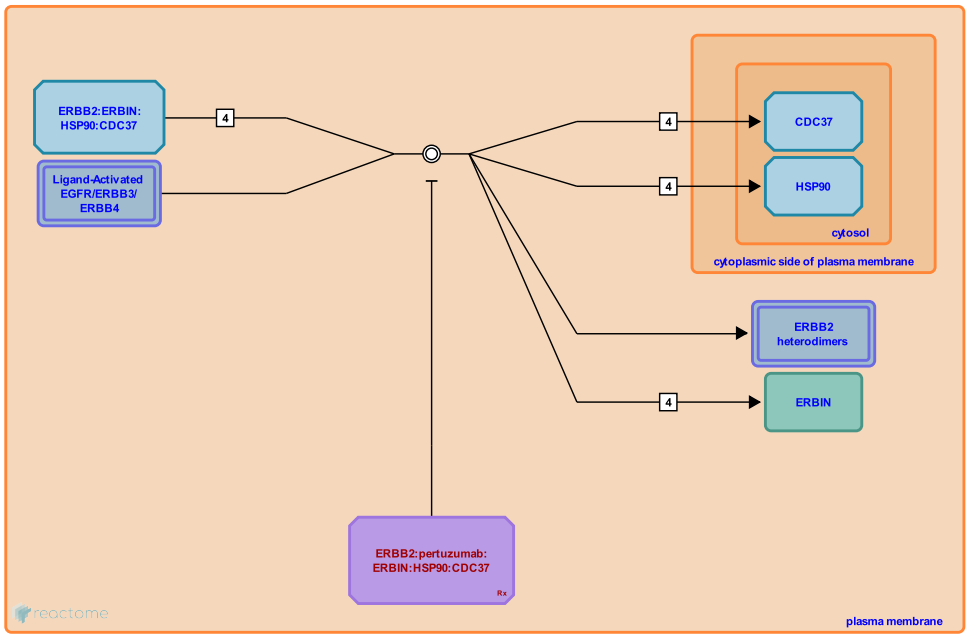
ERBB2 forms heterodimers with ligand-activated ERBB receptors: EGFR, ERBB3 and ERBB4 ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1963589

Type: dissociation

Compartments: plasma membrane, extracellular region, cytosol



ERBB2, which does not bind any known ligand, is activated through formation of a heterodimer with another ligand-activated ERBB family member. ERBB2 heterodimerization partners are EGF-stimulated EGFR (Wada et al. 1990, Karunagaran et al. 1996), ERBB3 stimulated by neuregulins NRG1 or NRG2 (Pinkas-Kramarski et al. 1996), and ERBB4 stimulated by neuregulins or EGF-like ligands (Li et al. 2007). In the process of dimerization, ERBB2 dissociates from chaperone proteins HSP90 and CDC37 (Xu et al 2001, Citri et al. 2004). Activated ERBB2 also dissociates from ERBB2IP, the protein responsible for proper localization of ERBB2 to basolateral membranes of epithelial cells (Borg et al. 2000).

Preceded by: ERBB3 binds neuregulins

Followed by: Trans-autophosphorylation of ERBB2 heterodimers, SRC family kinases phosphorylate ERBB2

Literature references

Ratzkin, BJ., Klapper, L., Levkowitz, G., Seger, R., Alroy, I., Waterman, H. et al. (1996). Diversification of Neu differentiation factor and epidermal growth factor signaling by combinatorial receptor interactions. *EMBO J, 15*, 2452-67. ↗

Beerli, RR., Ratzkin, BJ., Seger, R., Karunagaran, D., Chen, X., Hynes, NE. et al. (1996). ErbB-2 is a common auxiliary subunit of NDF and EGF receptors: implications for breast cancer. *EMBO J, 15*, 254-64. ↗

Gan, J., Szollosi, J., Yarden, Y., Vereb, G., Mosesson, Y., Citri, A. (2004). Hsp90 restrains ErbB-2/HER2 signalling by limiting heterodimer formation. *EMBO Rep, 5*, 1165-70. ↗

Mimnaugh, E., Rosser, MF., Neckers, LM., Yarden, Y., Nicchitta, C., Marcu, M. et al. (2001). Sensitivity of mature Erbb2 to geldanamycin is conferred by its kinase domain and is mediated by the chaperone protein Hsp90. *J Biol Chem, 276*, 3702-8. ↗

Mei, Y., Li, Z., Zhou, M., Liu, X. (2007). Neuregulin-1 only induces trans-phosphorylation between ErbB receptor heterodimer partners. *Cell Signal, 19*, 466-71. ↗

Editions

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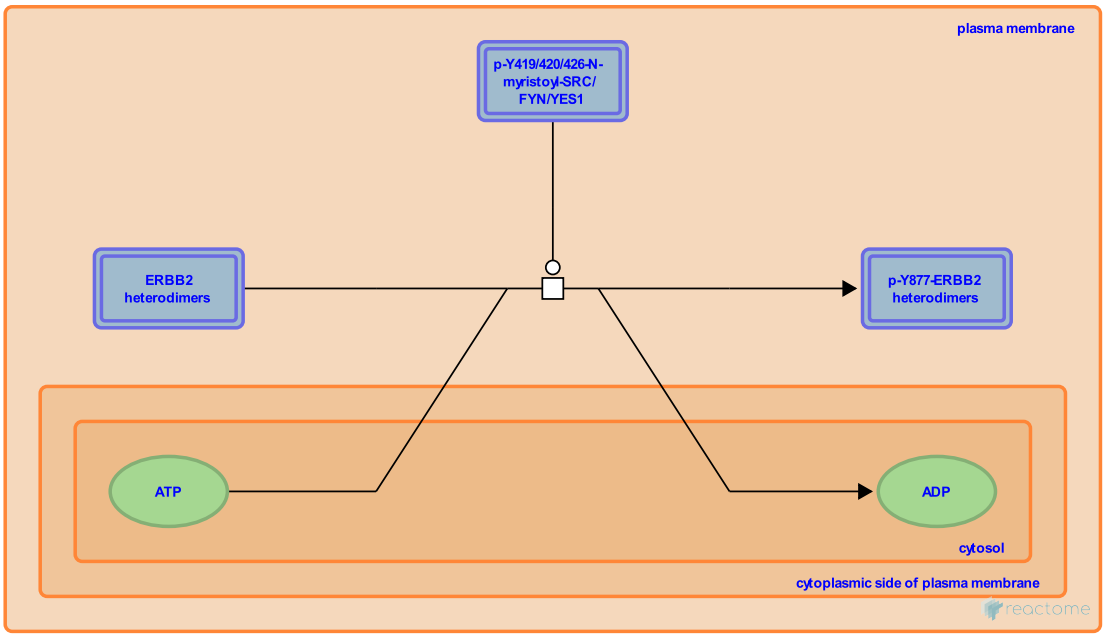
SRC family kinases phosphorylate ERBB2 ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1963586

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Dissociation of HSP90 from ERBB2 upon formation of ERBB2 heterodimers (with either EGFR, ERBB3 or ERBB4) enables phosphorylation of ERBB2 on the tyrosine residue Y877, mediated by one of SRC family kinases - SRC, FYN or YES1. Although not a mandatory prerequisite of ERBB2 catalytic activity, the phosphorylation at Y877 significantly increases the kinase activity of ERBB2.

Preceded by: ERBB2 forms heterodimers with ligand-activated ERBB receptors: EGFR, ERBB3 and ERBB4

Followed by: Trans-autophosphorylation of p-Y877-ERBB2 heterodimers

Literature references

Yuan, X., Xiang, Z., Beebe, K., Neckers, LM., Xu, W. (2007). Loss of Hsp90 association up-regulates Src-dependent ErbB2 activity. *Mol Cell Biol, 27*, 220-8. ↗

Editions

2011-11-04	Authored	Orlic-Milacic, M.
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2011-11-11	Reviewed	Neckers, LM., Xu, W.

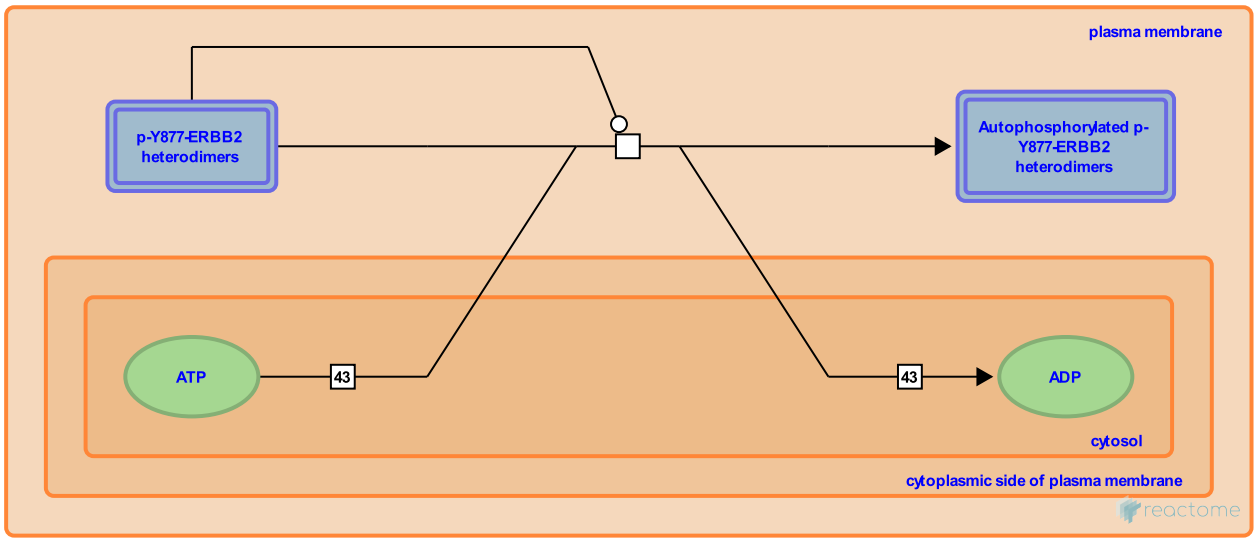
Trans-autophosphorylation of p-Y877-ERBB2 heterodimers ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1963581

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Phosphorylation of ERBB2 on tyrosine residue Y877 by SRC family kinases significantly increases trans-autophosphorylation rate of ERBB2 heterodimers, presumably by enabling the kinase domain of ERBB2 to achieve a conformation that positively affects ERBB2 kinase activity. The downstream signaling of phosphorylated ERBB2 heterodimers that are phosphorylated on Y877 of ERBB2, in addition to the known trans-autophosphorylation sites, has not been studied extensively; it is assumed that the behavior of Y877-phosphorylated ERBB2 heterodimers is qualitatively similar to the behavior of trans-autophosphorylated ERBB2 heterodimers which do not harbor this modification.

Preceded by: SRC family kinases phosphorylate ERBB2

Literature references

Yuan, X., Xiang, Z., Beebe, K., Neckers, LM., Xu, W. (2007). Loss of Hsp90 association up-regulates Src-dependent ErbB2 activity. *Mol Cell Biol, 27*, 220-8. ↗

Editions

2011-10-25	Edited	D'Eustachio, P.
2011-11-04	Authored	Orlic-Milacic, M.
2011-11-11	Reviewed	Neckers, LM., Xu, W.

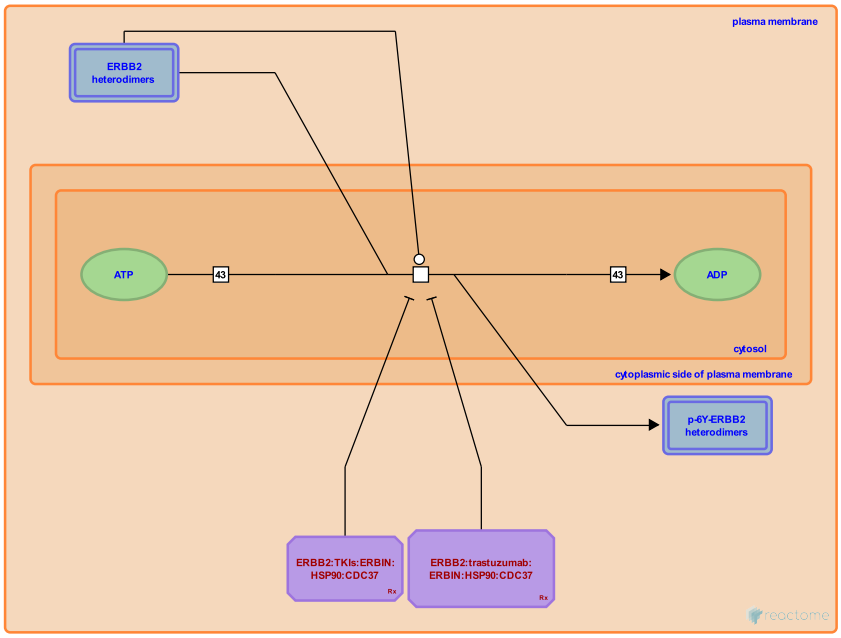
Trans-autophosphorylation of ERBB2 heterodimers ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1963582

Type: transition

Compartments: cytosol, extracellular region, plasma membrane



Dimers of ERBB2 and EGF-bound EGFR trans-autophosphorylate on six EGFR tyrosine residues and six ERBB2 tyrosine residues to form phosphorylated heterodimers that activate downstream signaling cascades (Ricci et al. 1995, Pinkas-Kramarski et al. 1996, Walton et al. 1990, Margolis et al. 1989, Hazan et al. 1990, Helin et al. 1991).

In heterodimers of ERBB2 and neuregulin-stimulated ERBB3, ERBB2 phosphorylates ERBB3 on tyrosine residues that serve as docking sites for the p85 subunit of PI3K (Y1054, Y1197, Y1222, Y1224, Y1260, Y1276 and Y1289), as well as SHC1 (Y1328) and GRB7 (Y1199 and Y1262). Since ERBB3 lacks catalytic activity, it cannot phosphorylate ERBB2. Hovewer, since ERBB2:ERBB3 heterodimers usually oligomerize on the cell surface, ERBB2 can become trans-autophosphorylated by an adjacent ERBB2 protein. It is not known if ERBB2 in the ERBB2:ERBB3 hetero-oligomer is phosphorylated on all conserved tyrosine residues and if the phosphorylation status of ERBB2 in the ERBB2:ERBB3 hetero-oligomer significantly affects signaling (Li et al. 2007, Pinkas-Kramarski et al. 1996, Prigent et al. 1994, Vijapurkar et al. 2003, Wallasch et al. 1995).

Heterodimers of ERBB2 and ERBB4 trans-autophosphorylate on tyrosine residues that serve as docking sites for PLC-gamma, GRB2 and SHC1, as well as p85 subunit of PI3K (PIK3R1) in the case of ERBB2 heterodimers with ERBB4 CYT1 isoforms (ERBB4cyt1) - ERBB4 JM-A CYT1 and ERBB4 JM-B-CYT1 (Li et al. 2007, Kaushansky et al. 2008, Hazan et al. 1990, Cohen et al. 1996).

Preceded by: ERBB2 forms heterodimers with ligand-activated ERBB receptors: EGFR, ERBB3 and ERBB4

Literature references

Fell, HP., Foy, L., Green, JM., Cohen, BD. (1996). HER4-mediated biological and biochemical properties in NIH 3T3 cells. Evidence for HER1-HER4 heterodimers. *J Biol Chem, 271*, 4813-8. ↗

Walton, GM., Rosenfeld, MG., Gill, GN., Chen, WS. (1990). Analysis of deletions of the carboxyl terminus of the epidermal growth factor receptor reveals self-phosphorylation at tyrosine 992 and enhanced in vivo tyrosine phosphorylation of cell substrates. *J Biol Chem, 265*, 1750-4. ↗

Schlessinger, J., Zilberstein, A., Hazan, R., Ullrich, A., Dombalagian, M., Margolis, B. (1990). Identification of autophosphorylation sites of HER2/neu. *Cell Growth Differ, 1*, 3-7. ↗

Beguinot, L., Helin, K. (1991). Internalization and down-regulation of the human epidermal growth factor receptor are regulated by the carboxyl-terminal tyrosines. *J Biol Chem, 266*, 8363-8. ↗

Mei, Y., Li, Z., Zhou, M., Liu, X. (2007). Neuregulin-1 only induces trans-phosphorylation between ErbB receptor heterodimer partners. *Cell Signal, 19*, 466-71. ↗

Editions

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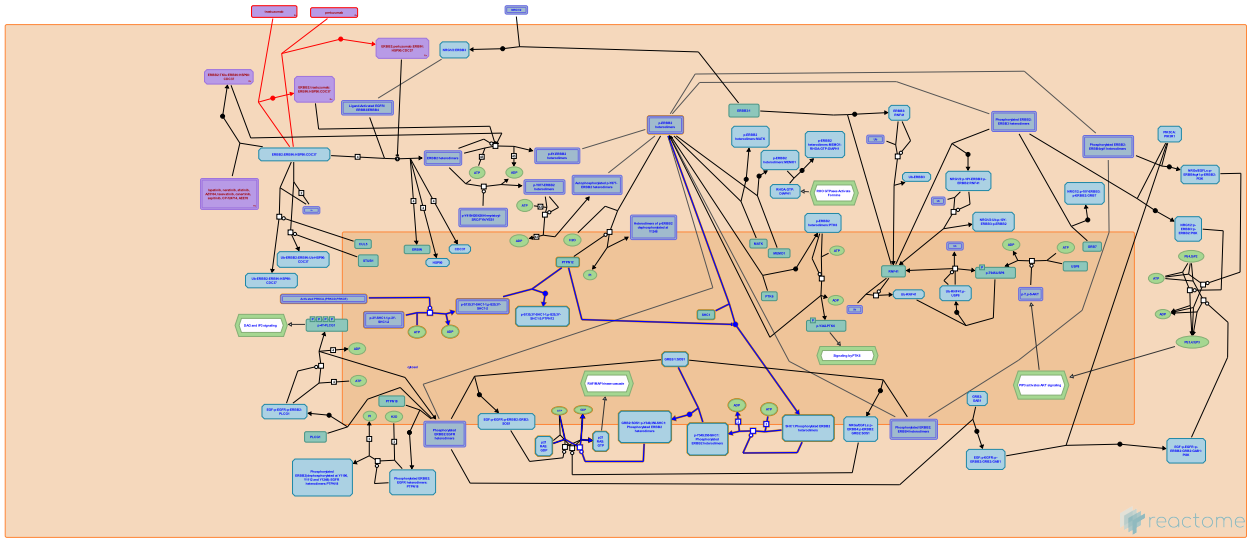
SHC1 events in ERBB2 signaling ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1250196

Compartments: plasma membrane, extracellular region, cytosol



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.

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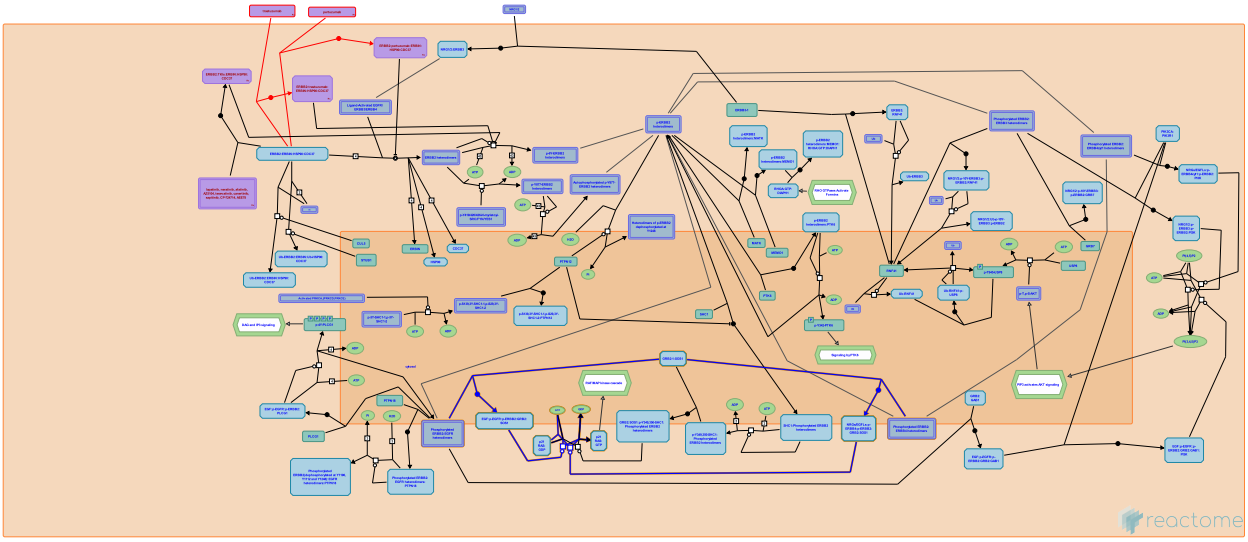
GRB2 events in ERBB2 signaling ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1963640



ERBB2:EGFR and ERBB2:ERBB4 can directly recruit GRB2:SOS1 complex through phosphorylated C-tail tyrosines of EGFR (Y1068 and Y1086) and ERBB2 (Y1139) that serve as docking sites for GRB2 (Xie et al. 1995, Sepp-Lorenzino et al. 1996), which, again, results in SOS1-mediated guanyl-nucleotide exchange on RAS and activation of RAF and MAP kinases (Janes et al. 1994, Sepp-Lorenzino et al. 1996).

Editions

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2011-11-07	Edited	D'Eustachio, P., Matthews, L.
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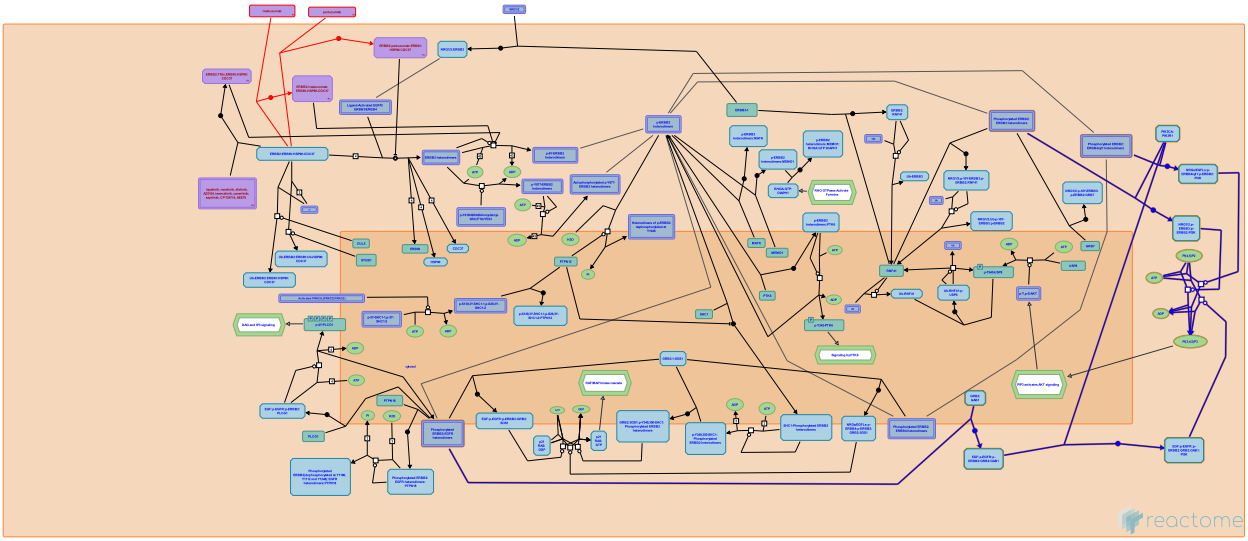
PI3K events in ERBB2 signaling ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1963642



ERBB2:ERBB3 and ERBB2:ERBB4cyt1 heterodimers activate PI3K signaling by direct binding of PI3K regulatory subunit p85 (Yang et al. 2007, Cohen et al. 1996, Kaushansky et al. 2008) to phosphorylated tyrosine residues in the C-tail of ERBB3 (Y1054, Y1197, Y1222, Y1224, Y1276 and Y1289) and ERBB4 CYT1 isoforms (Y1056 in JM-A CYT1 isoform and Y1046 in JM-B CYT1 isoform). Regulatory subunit p85 subsequently recruits catalytic subunit p110 of PI3K, resulting in the formation of active PI3K, conversion of PIP2 to PIP3, and PIP3-mediated activation of AKT signaling (Junttila et al. 2009, Kainulainen et al. 2000). Heterodimers of ERBB2 and EGFR recruit PI3K indirectly, through GRB2:GAB1 complex (Jackson et al. 2004), which again leads to PIP3-mediated activation of AKT signaling.

Editions

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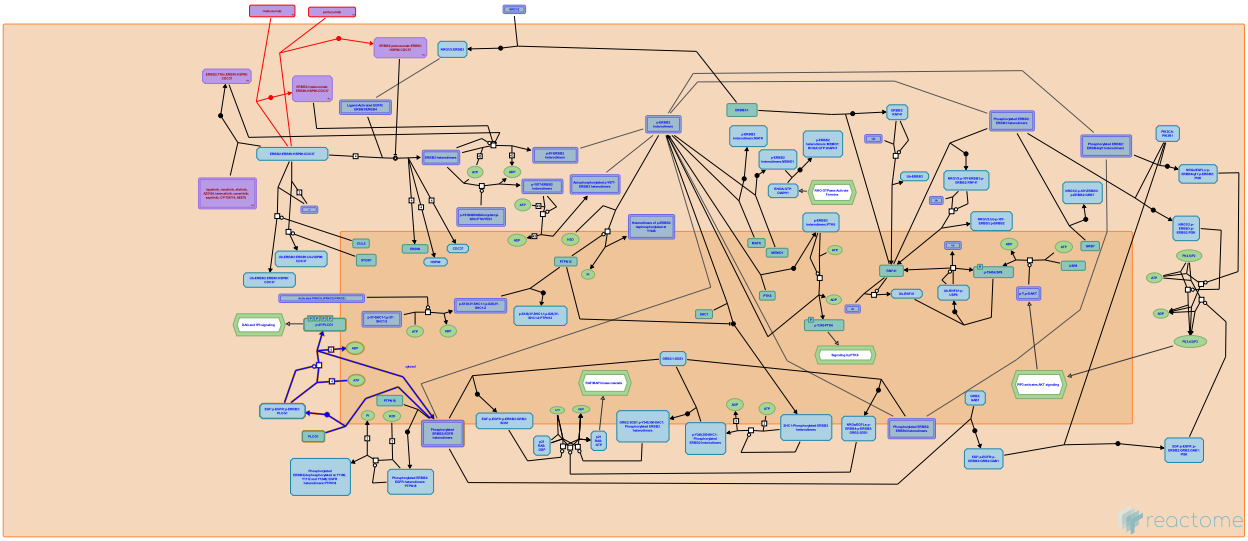
2011-11-07	Edited	D'Eustachio, P., Matthews, L.
2011-11-11	Reviewed	Neckers, LM., Xu, W.

PLCG1 events in ERBB2 signaling ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1251932



Activation of PLCG1 signaling is observed only in the presence of ERBB2:EGFR heterodimers, with PLCG1 binding to phosphorylated tyrosine Y992 and Y1173 in the C-tail of EGFR (Chattopadhyay et al. 1999), and potentially Y1023 in the C-tail of ERBB2 (Fazioli et al. 1991, Cohen et al. 1996).

Editions

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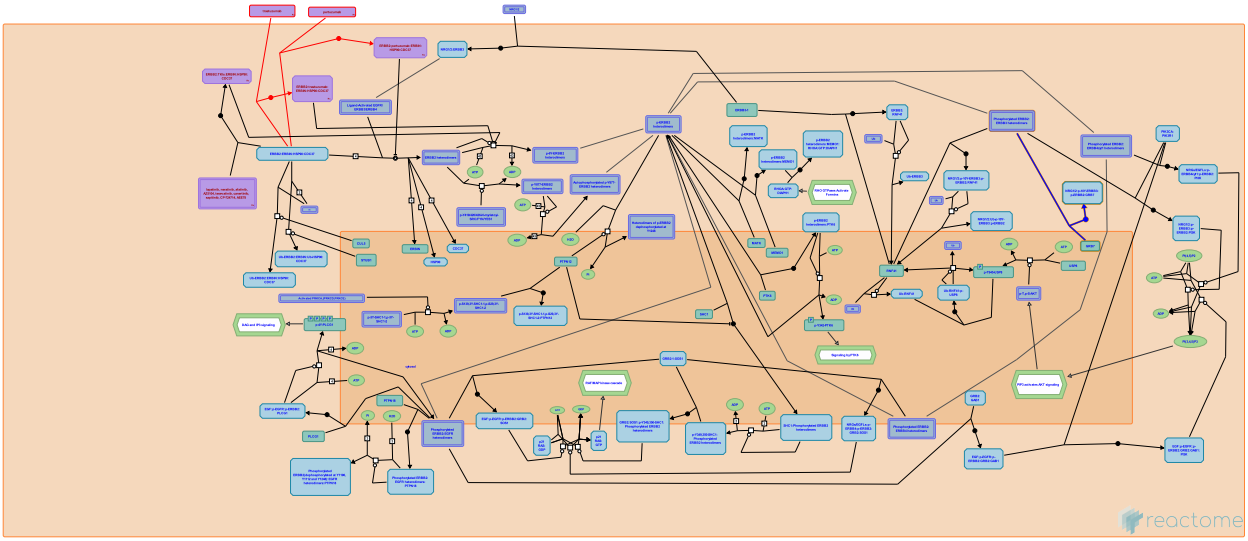
2011-11-07	Edited	D'Eustachio, P., Matthews, L.
2011-11-11	Reviewed	Neckers, LM., Xu, W.

GRB7 events in ERBB2 signaling ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-1306955



Heterodimers of ERBB2 and ERBB3 are able to bind GRB7 (Fiddes et al. 1998) through phosphorylated tyrosine residues in the C-tail of ERBB3 (Y1199 and Y1262) (Fiddes et al. 1998), but the exact downstream signaling of this complex has not been elucidated. GRB7 can recruit SHC1 to the active ERBB2 complex, and contributes to ERBB2 signaling-induced RAS activation, which promotes cellular proliferation, but the exact mechanism has not been elucidated (Pradip et al. 2013). In addition, GRB7 can be phosphorylated by the integrin-activated PTK2 (FAK), leading to VAV2-dependent activation of RAC1 and promotion of cell migration. The exact mechanistic details of GRB7-induced RAC1 activation are not known (Pradip et al. 2013).

Literature references

Leyland-Jones, B., Bouzyk, M., Dey, N., Pradip, D. (2013). Dissecting GRB7-mediated signals for proliferation and migration in HER2 overexpressing breast tumor cells: GTP-ase rules. *Am J Cancer Res, 3*, 173-95. ↗

Daly, RJ., Campbell, DH., Wallasch, C., Sasaki, H., Janes, PW., Fiddes, RJ. et al. (1998). Analysis of Grb7 recruitment by heregulin-activated erbB receptors reveals a novel target selectivity for erbB3. *J Biol Chem, 273*, 7717-24. ↗

Editions

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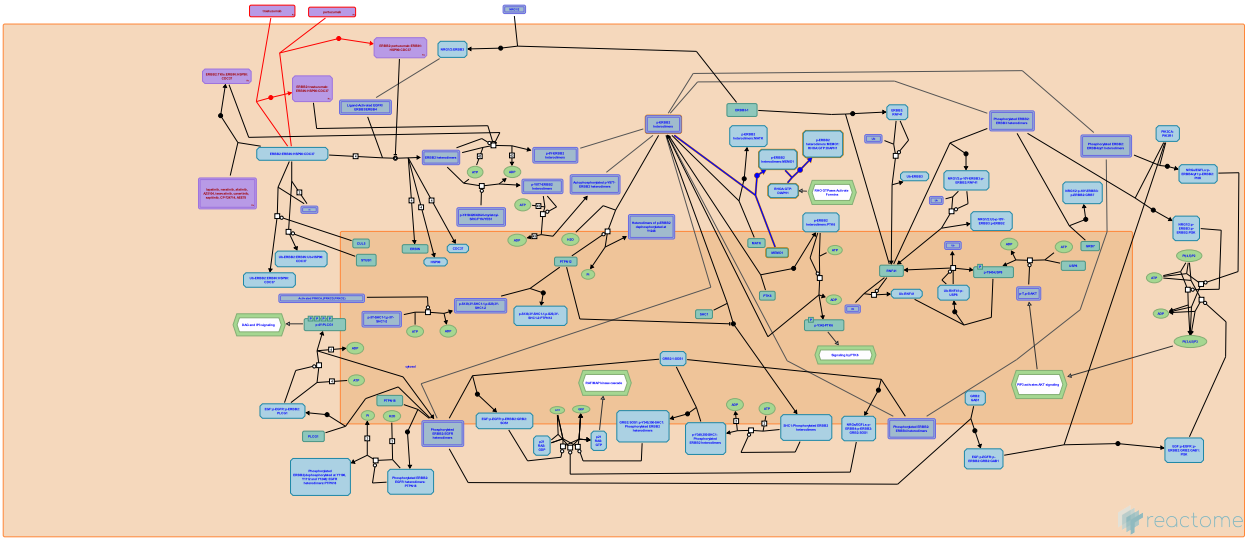
ERBB2 Regulates Cell Motility ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-6785631



Activated ERBB2 heterodimers regulate cell motility through association with MEMO1. MEMO1 retains activated RHOA GTPase and its associated protein DIAPH1 at the plasma membrane, thus linking ERBB2 activation with the microtubule and actin dynamics downstream of the RHOA:GTP:DIAPH1 complex (Marone et al. 2004, Qiu et al. 2008, Zaoui et al. 2008, Zaoui et al. 2010).

Literature references

Zaoui, K., Benseddik, K., Salaün, D., Daou, P., Badache, A. (2010). ErbB2 receptor controls microtubule capture by recruiting ACF7 to the plasma membrane of migrating cells. *Proc. Natl. Acad. Sci. U.S.A., 107*, 18517-22. ↗

Leahy, DJ., Hynes, NE., Qiu, C., Lienhard, S., Badache, A. (2008). Memo is homologous to nonheme iron dioxygenases and binds an ErbB2-derived phosphopeptide in its vestigial active site. *J. Biol. Chem., 283*, 2734-40. ↗

Zaoui, K., Isnardon, D., Honoré, S., Braguer, D., Badache, A. (2008). Memo-RhoA-mDia1 signaling controls microtubules, the actin network, and adhesion site formation in migrating cells. *J. Cell Biol., 183*, 401-8. ↗

Dankort, D., Hess, D., Muller, WJ., Marone, R., Hynes, NE., Badache, A. (2004). Memo mediates ErbB2-driven cell motility. *Nat. Cell Biol., 6*, 515-22. ↗

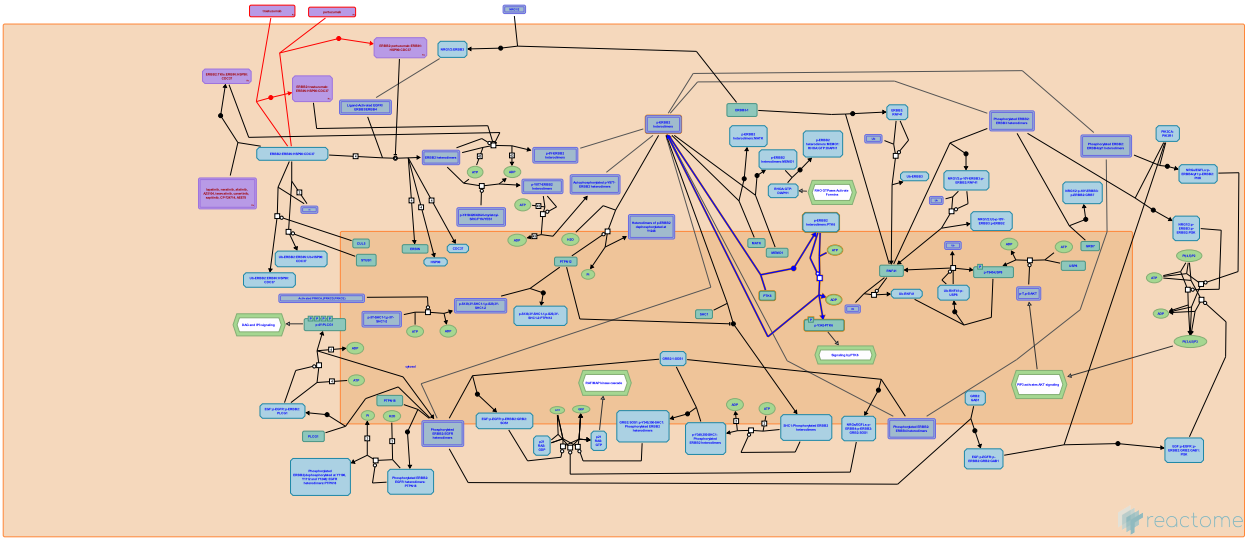
Editions

2016-01-28	Authored, Edited	Orlic-Milacic, M.
2016-02-03	Reviewed	Badache, A.

ERBB2 Activates PTK6 Signaling ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-8847993



PTK6 (BRK) is activated downstream of ERBB2 (HER) (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). However, it is not clear if MET and EGFR activate PTK6 directly or act through ERBB2, since it is known that ERBB2 forms heterodimers with EGFR (Spivak-Kroizman et al. 1992), and MET can heterodimerize with both EGFR and ERBB2 (Tanizaki et al. 2011).

Literature references

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

Peng, M., Tyner, AL., Ball-Kell, SM. (2015). Protein tyrosine kinase 6 promotes ERBB2-induced mammary gland tumorigenesis in the mouse. *Cell Death Dis, 6*, e1848. ↗

Nakagawa, K., Tanizaki, J., Okamoto, I., Sakai, K. (2011). Differential roles of trans-phosphorylated EGFR, HER2, HER3, and RET as heterodimerisation partners of MET in lung cancer with MET amplification. *Br. J. Cancer, 105*, 807-13. ↗

Gusterson, BA., Jackson, LE., Crompton, MR., Kamalati, T., Jolin, HE., Dean, CJ. et al. (1996). Brk, a breast tumor-derived non-receptor protein-tyrosine kinase, sensitizes mammary epithelial cells to epidermal growth factor. *J. Biol. Chem., 271*, 30956-63. ↗

Muthuswamy, SK., Xiang, B., Lakshmi, B., Yu, M., Miller, WT., Krasnitz, A. et al. (2008). Brk is coamplified with ErbB2 to promote proliferation in breast cancer. *Proc. Natl. Acad. Sci. U.S.A., 105*, 12463-8. ↗

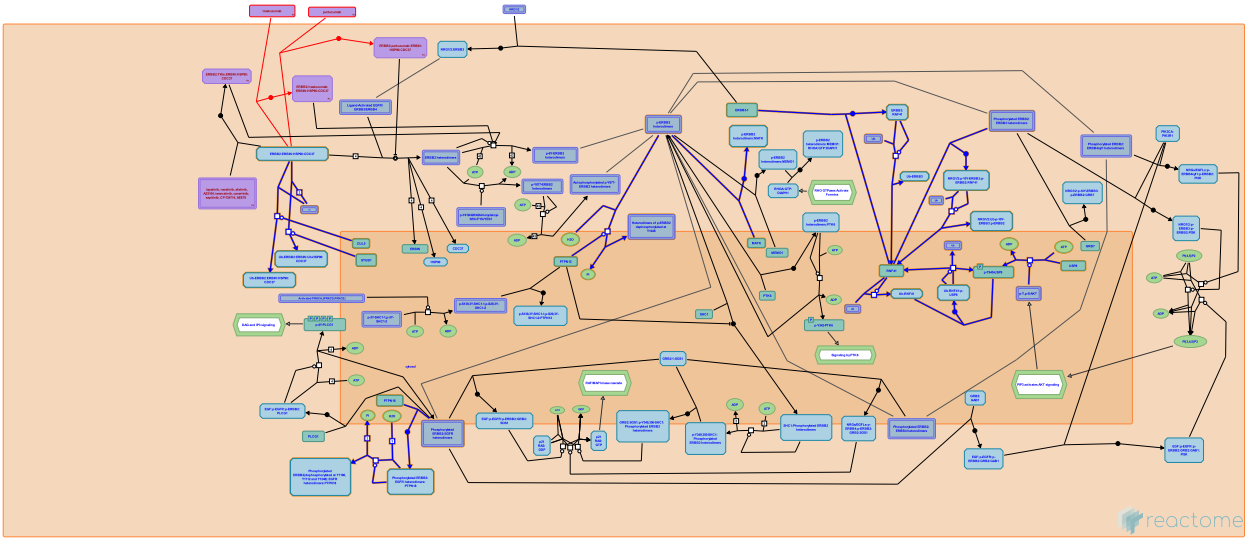
Editions

2016-01-05	Authored, Edited	Orlic-Milacic, M.
2016-02-07	Reviewed	Pires, IM.

Downregulation of ERBB2 signaling ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-8863795



Signaling by ERBB2 can be downregulated by ubiquitination and subsequent proteasome-dependent degradation of ERBB2 or activated ERBB2 heterodimers. In addition, protein tyrosine phosphatases that dephosphorylate tyrosine residues in the C-terminus of ERBB2 prevent the recruitment of adapter proteins involved in signal transduction, thus attenuating ERBB2 signaling.
STUB1 (CHIP) and CUL5 are E3 ubiquitin ligases that can target non-activated ERBB2 for proteasome-dependent degradation (Xu et al. 2002, Ehrlich et al. 2009). RNF41 (NRDP1) is an E3 ubiquitin ligase that targets ERBB3 and activated heterodimers of ERBB2 and ERBB3 for proteasome-dependent degradation by ubiquitinating ERBB3 (Cao et al. 2007).
Two protein tyrosine phosphatases of the PEST family, PTPN12 and PTPN18, dephosphorylate tyrosine residues in the C-terminus of ERBB2, thus preventing signal transduction to RAS and PI3K effectors (Sun et al. 2011, Wang et al. 2014).

Literature references

Mimnaugh, E., Yuan, X., Neckers, LM., Marcu, M., Xu, W., Patterson, C. (2002). Chaperone-dependent E3 ubiquitin ligase CHIP mediates a degradative pathway for c-ErbB2/Neu. *Proc Natl Acad Sci U S A, 99*, 12847-52. ↗

Schmitt, E., Creighton, CJ., Hilsenbeck, SG., Gygi, SP., Bernardi, RJ., Osborne, CK. et al. (2011). Activation of multiple proto-oncogenic tyrosine kinases in breast cancer via loss of the PTPN12 phosphatase. *Cell, 144*, 703-18. ↗

Yang, F., Zhang, Y., Yang, DX., Wang, HM., Ning, SL., Sun, JP. et al. (2014). The catalytic region and PEST domain of PTPN18 distinctly regulate the HER2 phosphorylation and ubiquitination barcodes. *Cell Res., 24*, 1067-90. ↗

Yu, XF., Luo, K., Xiao, Z., Neckers, LM., Martinez, T., Xu, W. et al. (2009). Regulation of Hsp90 client proteins by a Cullin5-RING E3 ubiquitin ligase. *Proc Natl Acad Sci U S A, 106*, 20330-5. ↗

Carraway KL, 3rd., Cao, Z., Sweeney, C., Wu, X., Yen, L. (2007). Neuregulin-induced ErbB3 downregulation is mediated by a protein stability cascade involving the E3 ubiquitin ligase Nrdp1. *Mol Cell Biol, 27*, 2180-8. ↗

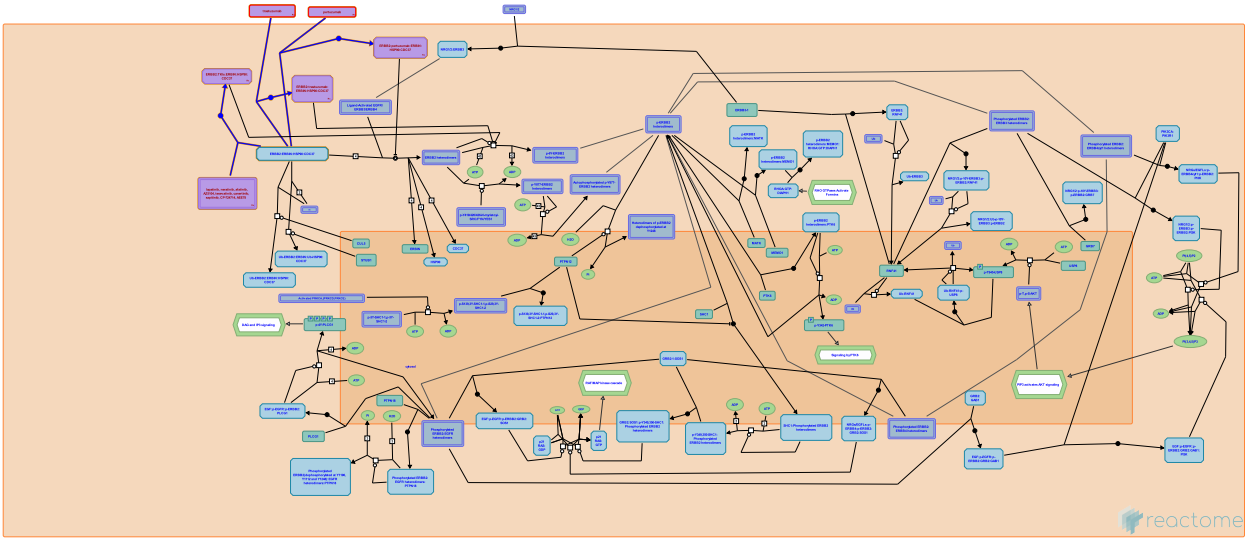
Editions

2016-08-11	Reviewed	Matthews, L.
2016-08-12	Authored, Edited	Orlic-Milacic, M.

Drug-mediated inhibition of ERBB2 signaling ↗

Location: Signaling by ERBB2

Stable identifier: R-HSA-9652282



Signaling by ERBB2 can be pharmacologically inhibited with tyrosine kinase inhibitors (TKIs) (Nelson and Fry 2001, Xia et al. 2002, Wood et al. 2004, Rabindran et al. 2004, Gandreau et al. 2007, Jani et al. 2007, Li et al. 2008, Hichkinson et al. 2010, Traxler et al. 2014, Hanker et al. 2017), and therapeutic antibodies, such as trastuzumab (Hudziak et al. 1989, Carter et al. 1992, Pickl and Ries 2009, Maadi et al. 2018) and pertuzumab (Franklin et al. 2004).

Literature references

Jackman, L., Ventura, R., Shi, Y., De Costa, A., Zhang, W., Keast, P. et al. (2007). Inhibition of the T790M gatekeeper mutant of the epidermal growth factor receptor by EXEL-7647. *Clin. Cancer Res., 13*, 3713-23. ↗

Spector, NL., Alligood, KJ., Rusnak, DW., Liu, LH., Keith, BR., Owens, G. et al. (2002). Anti-tumor activity of GW572016: a dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways. *Oncogene, 21*, 6255-63. ↗

Sliwkowski, MX., Leahy, DJ., Vajdos, FF., de Vos, AM., Carey, KD., Franklin, MC. (2004). Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell, 5*, 317-28. ↗

Ogilvie, D., Smith, P., Speake, G., Anderton, J., Beck, S., Wilkinson, RW. et al. (2010). AZD8931, an equipotent, reversible inhibitor of signaling by epidermal growth factor receptor, ERBB2 (HER2), and ERBB3: a unique agent for simultaneous ERBB receptor blockade in cancer. *Clin. Cancer Res., 16*, 1159-69. ↗

Fendly, BM., Shepard, HM., Winget, M., Hudziak, RM., Lewis, GD., Ullrich, A. (1989). p185HER2 monoclonal antibody has antiproliferative effects in vitro and sensitizes human breast tumor cells to tumor necrosis factor. *Mol. Cell. Biol., 9*, 1165-72. ↗

Editions

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2019-11-01	Edited	Orlic-Milacic, M.
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