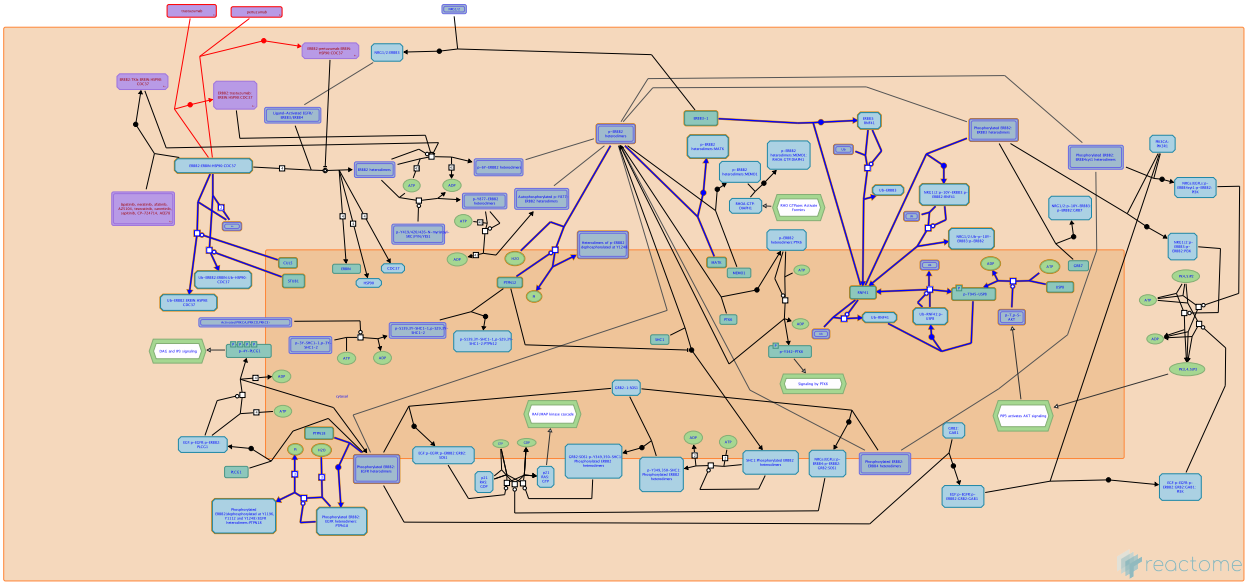
Downregulation of ERBB2 signaling



Ayoub, E., D'Eustachio, P., Matthews, L., Neckers, LM., Orlic-Milacic, M., Tremblay, M., Xu, W.

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

21/09/2021

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. ↗

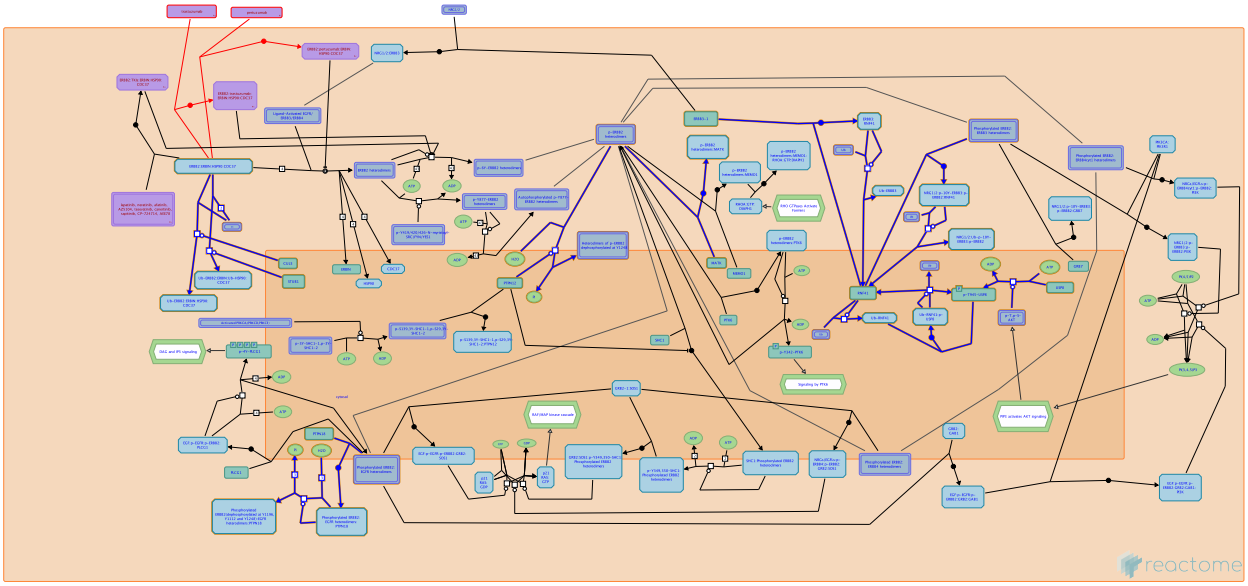
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Downregulation of ERBB2 signaling ↗

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

Ehrlich, ES., Wang, T., Luo, K., Xiao, Z., Niewiadomska, AM., Martinez, T. 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. ↗

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

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

Sun, T., Aceto, N., Meerbrey, KL., Kessler, JD., Zhou, C., Migliaccio, I. et al. (2011). Activation of multiple proto-oncogenic tyrosine kinases in breast cancer via loss of the PTPN12 phosphatase. *Cell, 144*, 703-18. ↗

Xu, W., Marcu, M., Yuan, X., Mimnaugh, E., Patterson, C., Neckers, LM. (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. ↗

Editions

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

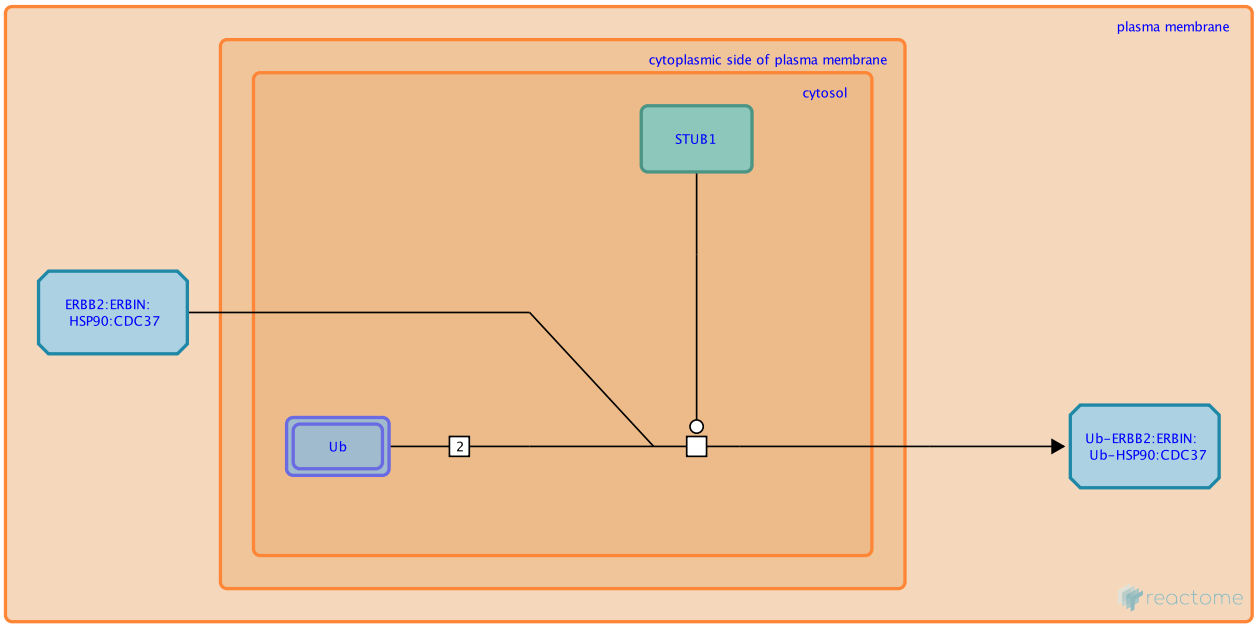
CHIP (STUB1) mediates ubiquitination of ERBB2

Location: Downregulation of ERBB2 signaling

Stable identifier: R-HSA-1918092

Type: transition

Compartments: cytosol, plasma membrane



E3 ubiquitin ligase CHIP (STUB1) mediates ERBB2 ubiquitination by associating with the ERBB2 indirectly, through the chaperone protein HSP90. CHIP (STUB1) ubiquitinates both ERBB2 and HSP90, leading to their proteasome-dependent degradation. Ubiquitination of ERBB2 by CHIP (STUB1) is independent of ERBB2 activation.

Literature references

Xu, W., Marcu, M., Yuan, X., Mimnaugh, E., Patterson, C., Neckers, LM. (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.

Editions

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

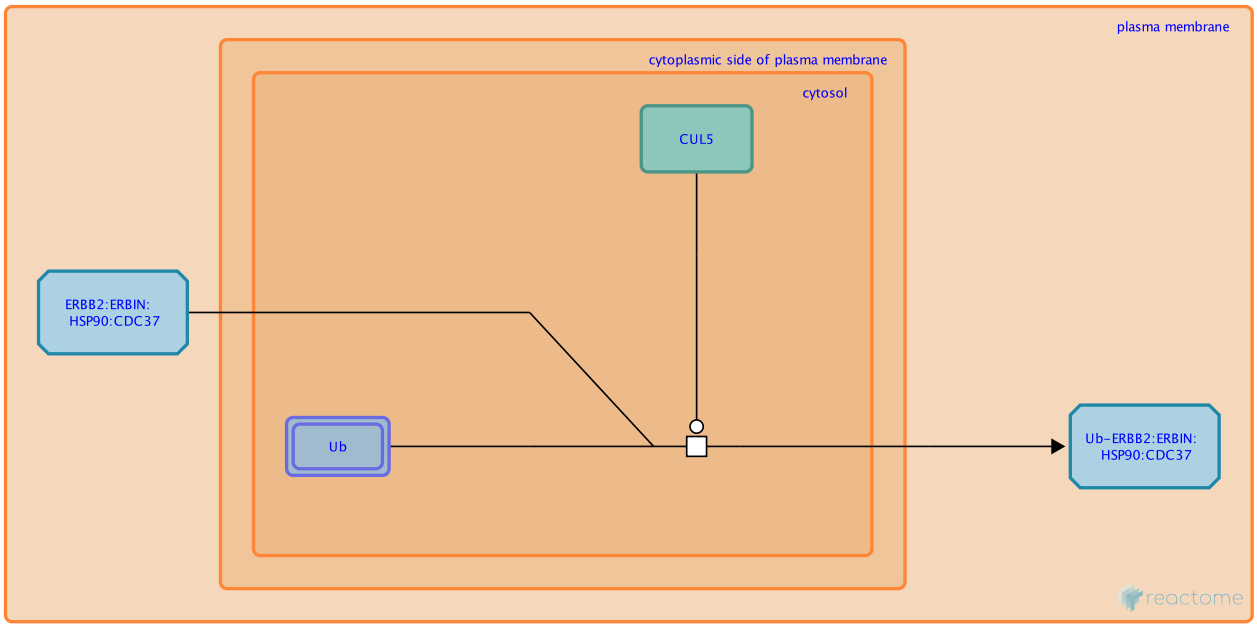
CUL5 mediates ubiquitination of ERBB2 ↗

Location: Downregulation of ERBB2 signaling

Stable identifier: R-HSA-1918095

Type: transition

Compartments: cytosol, plasma membrane



E3 ubiquitin ligase Cullin-5 (CUL5) is recruited to the ERBB2 site at the plasma membrane and ubiquitinates ERBB2 in an HSP90-dependent way, targeting it for degradation. Ubiquitination of ERBB2 by CUL5 appears to be independent of CUL5 adaptor proteins ElonginB and ElonginC.

Literature references

Ehrlich, ES., Wang, T., Luo, K., Xiao, Z., Niewiadomska, AM., Martinez, T. 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. ↗

Editions

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

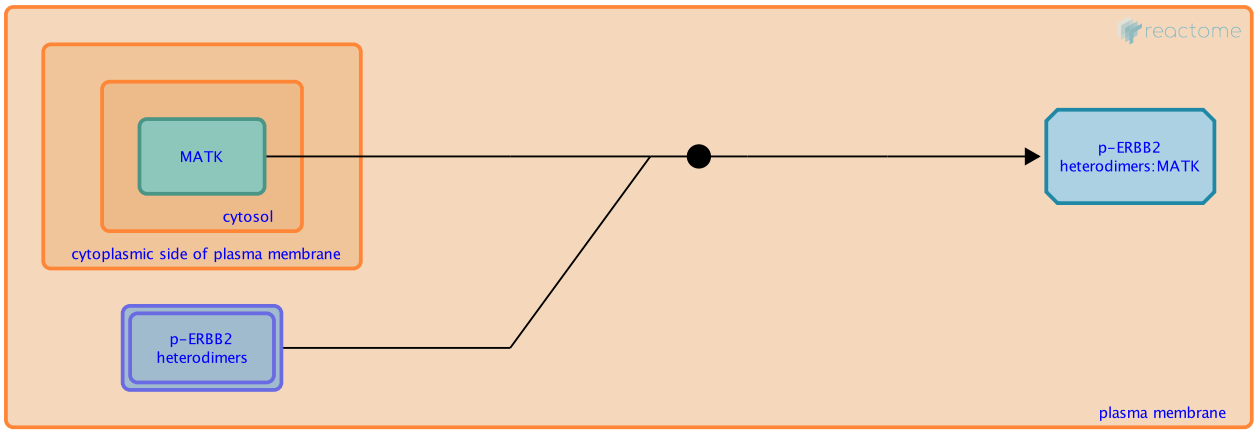
MATK (CSK homologous kinase) binds phosphorylated ERBB2 ↗

Location: Downregulation of ERBB2 signaling

Stable identifier: R-HSA-1963563

Type: binding

Compartments: plasma membrane, cytosol, extracellular region



MATK (also known as CHK or CSK homologous kinase) binds to ERBB2 through phosphorylated tyrosine residue Y1253 in the C-tail of ERBB2 and, through an unknown mechanism, inhibits ERBB2 downstream signaling.

Literature references

Zrihan-Licht, S., Deng, B., Yarden, Y., McShan, G., Keydar, I., Avraham, H. (1998). Csk homologous kinase, a novel signaling molecule, directly associates with the activated ErbB-2 receptor in breast cancer cells and inhibits their proliferation. *J Biol Chem, 273*, 4065-72. ↗

Editions

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

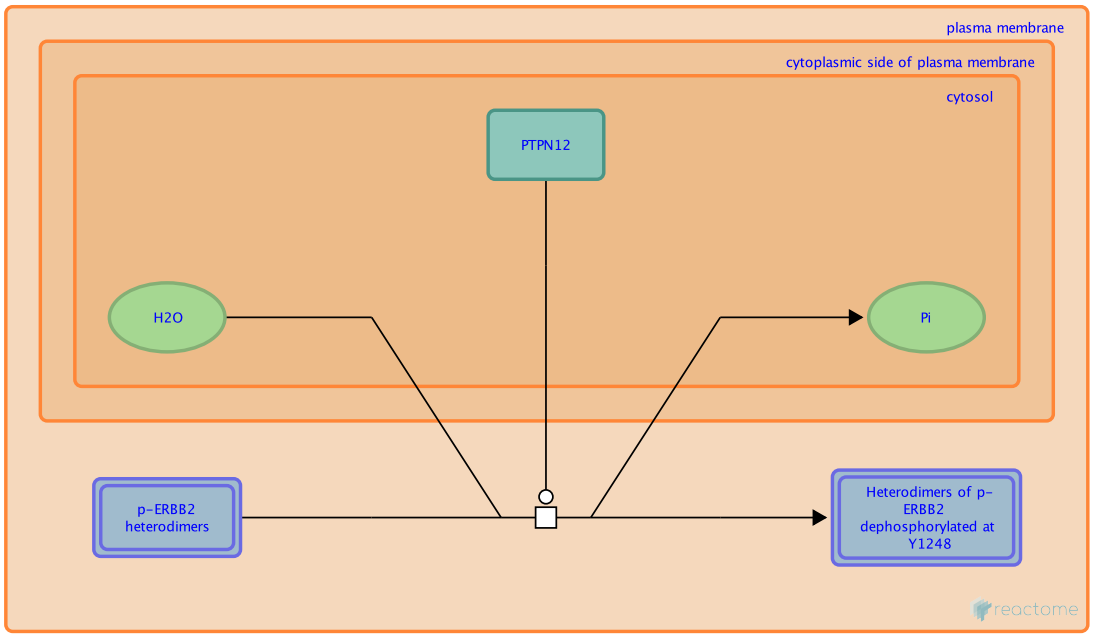
PTPN12 dephosphorylates ERBB2 on tyrosine Y1248 ↗

Location: Downregulation of ERBB2 signaling

Stable identifier: R-HSA-8863804

Type: transition

Compartments: plasma membrane, cytosol



PTPN12 protein tyrosine phosphatase dephosphorylates activated ERBB2 at tyrosine residue Y1248 and activated EGFR at tyrosine residue Y1148 (Y1148 corresponds to Y1172 of the nascent EGFR, with 24 amino acid signal peptide at the N-terminus). PTPN12-mediated dephosphorylation of ERBB2 attenuates downstream RAS activation, as Y1248 is involved in SHC1 recruitment. Similar to Y1148 of EGFR, Y1248 of ERBB2 is part of the NPXY motif that is, when phosphorylated on the tyrosine residue, recognized by the N-terminal phosphotyrosine interaction domain (PID) of SHC1 (Batzer et al. 1995, Songyang et al. 1995). SHC1 itself could be a target for PTPN12. PTPN12 function is frequently lost in triple negative breast cancer (Sun et al. 2011).

Literature references

Sun, T., Aceto, N., Meerbrey, KL., Kessler, JD., Zhou, C., Migliaccio, I. et al. (2011). Activation of multiple proto-oncogenic tyrosine kinases in breast cancer via loss of the PTPN12 phosphatase. *Cell, 144*, 703-18. ↗

Songyang, Z., Margolis, B., Chaudhuri, M., Shoelson, SE., Cantley, LC. (1995). The phosphotyrosine interaction domain of SHC recognizes tyrosine-phosphorylated NPXY motif. *J. Biol. Chem., 270*, 14863-6. ↗

Batzer, AG., Blaikie, P., Nelson, K., Schlessinger, J., Margolis, B. (1995). The phosphotyrosine interaction domain of Shc binds an LXNPXY motif on the epidermal growth factor receptor. *Mol. Cell. Biol., 15*, 4403-9. ↗

Editions

2016-03-10	Authored	Orlic-Milacic, M.
2016-08-04	Reviewed	Tremblay, M., Ayoub, E.
2016-08-09	Edited	Orlic-Milacic, M.

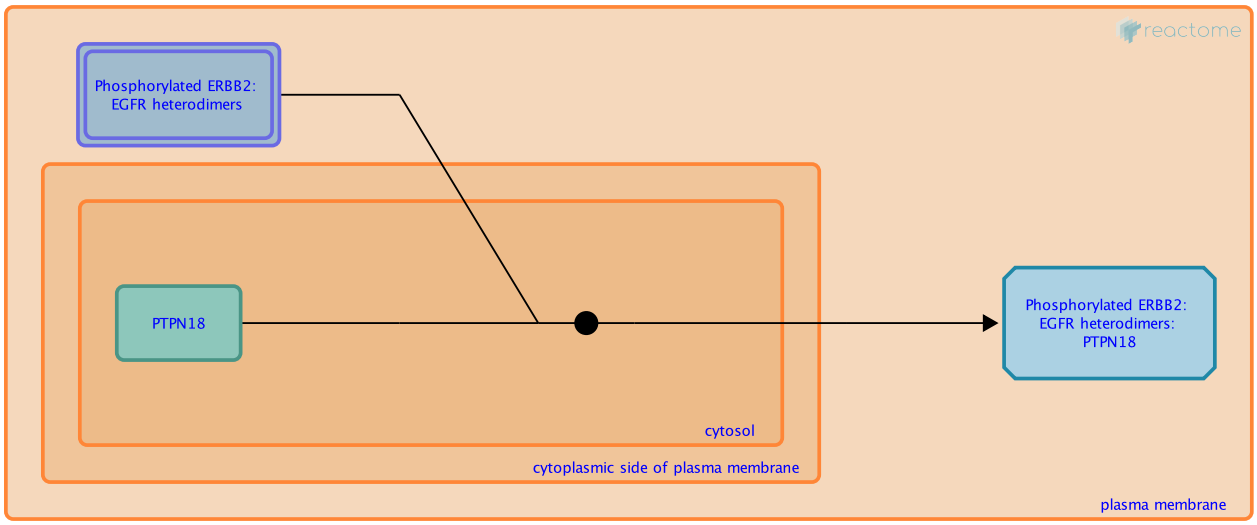
PTPN18 binds ERBB2:EGFR heterodimers ↗

Location: Downregulation of ERBB2 signaling

Stable identifier: R-HSA-8864105

Type: binding

Compartments: cytosol, plasma membrane



PTPN18 protein tyrosine phosphatase (BDP1) binds ERBB2, activated in response to EGF stimulation, via PEST and catalytic domains of PTPN18 (Wang et al. 2014).

Followed by: PTPN18 dephosphorylates ERBB2 at Y1196, Y1112 and Y1248

Literature references

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

Editions

2016-03-12	Authored	Orlic-Milacic, M.
2016-08-04	Reviewed	Tremblay, M., Ayoub, E.
2016-08-09	Edited	Orlic-Milacic, M.

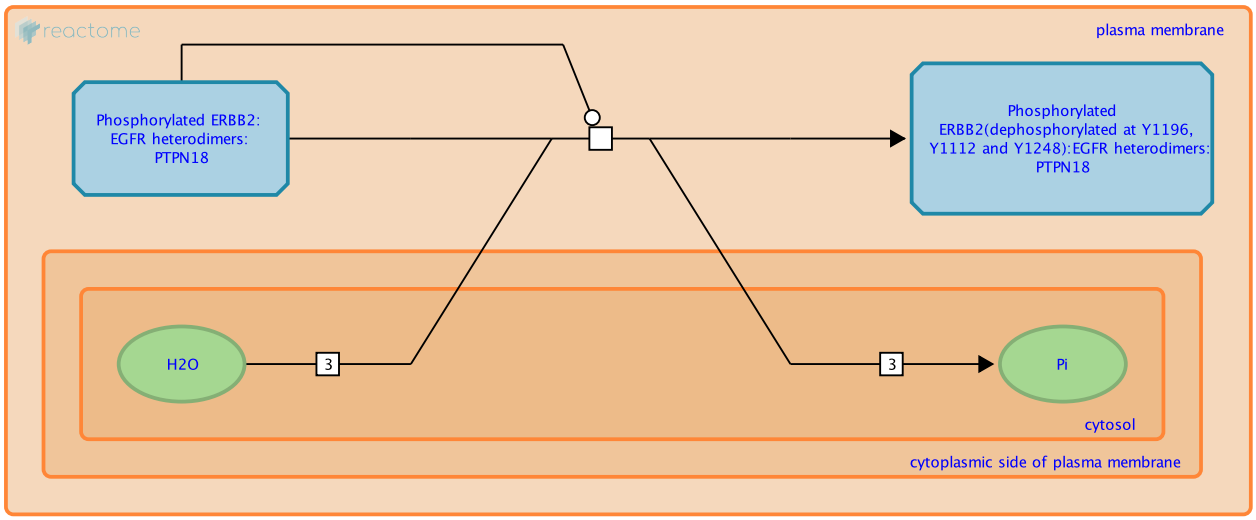
PTPN18 dephosphorylates ERBB2 at Y1196, Y1112 and Y1248 ↗

Location: Downregulation of ERBB2 signaling

Stable identifier: R-HSA-8864125

Type: transition

Compartments: plasma membrane



Protein tyrosine kinase PTPN18 dephosphorylates ERBB2, activated in response to EGF stimulation (Gensler et al. 2004), at tyrosine residues Y1196, Y1112 and Y1248 (Wang et al. 2014). PTPN18 does not dephosphorylate activated EGFR. Dephosphorylation of ERBB2 tyrosines Y1196 and Y1248 attenuates downstream activation of PI3K/AKT and RAS signaling. Dephosphorylation of Y1112 interferes with the recruitment of CBL E3 ubiquitin ligase to activated ERBB2 and CBL-mediated lysosomal route of ERBB2 down-regulation. When phosphorylated by an unknown serine/threonine kinase in an AKT-dependent manner on serine residues S419 and S423, PTPN18 recruits beta-TRCP ubiquitin ligase complex to ERBB2, thus promoting proteasome-dependent ERBB2 degradation (Wang et al. 2014).

Preceded by: PTPN18 binds ERBB2:EGFR heterodimers

Literature references

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

Gensler, M., Buschbeck, M., Ullrich, A. (2004). Negative regulation of HER2 signaling by the PEST-type protein-tyrosine phosphatase BDP1. *J. Biol. Chem., 279*, 12110-6. ↗

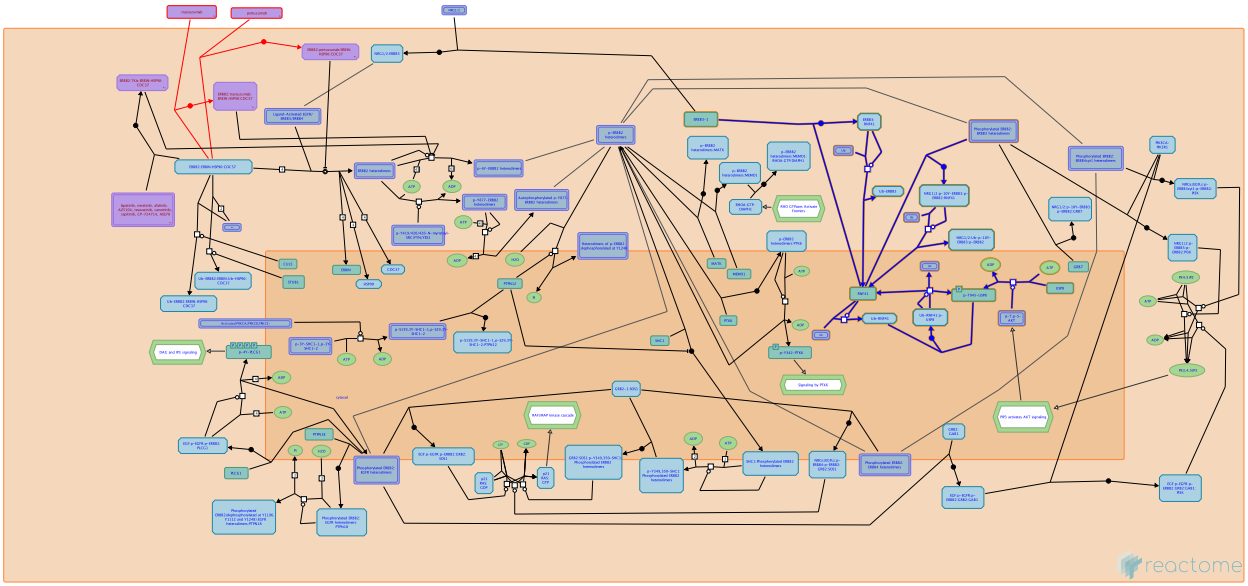
Editions

2016-03-12	Authored	Orlic-Milacic, M.
2016-08-04	Reviewed	Tremblay, M., Ayoub, E.
2016-08-09	Edited	Orlic-Milacic, M.

Downregulation of ERBB2:ERBB3 signaling ↗

Location: Downregulation of ERBB2 signaling

Stable identifier: R-HSA-1358803



Level of plasma membrane ERBB3 is regulated by E3 ubiquitin ligase RNF41 (also known as NRDP1), which binds and ubiquitinates both inactive and activated ERBB3, targeting it for degradation (Cao et al. 2007). RNF41 is subject to self-ubiquitination which keeps its levels low when ERBB3 is not stimulated, and preserves ERBB3 expression on the cell surface (Qiu et al. 2002). Self-ubiquitination of RNF41 is reversible, through the action of ubiquitin protease USP8, an enzyme stabilized by AKT-mediated phosphorylation. Therefore, activation of AKT by ERBB2:ERBB3 signaling leads to phosphorylation of USP8 (Cao et al. 2007), which increases level of RNF41 through deubiquitination, and results in degradation of activated ERBB3 (Cao et al. 2007) - a negative feedback loop of ERBB3 signaling. Downregulation of EGFR and ERBB4 signaling is explained in pathways Signaling by EGFR and 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.

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