Downregulation of ERBB4 signaling
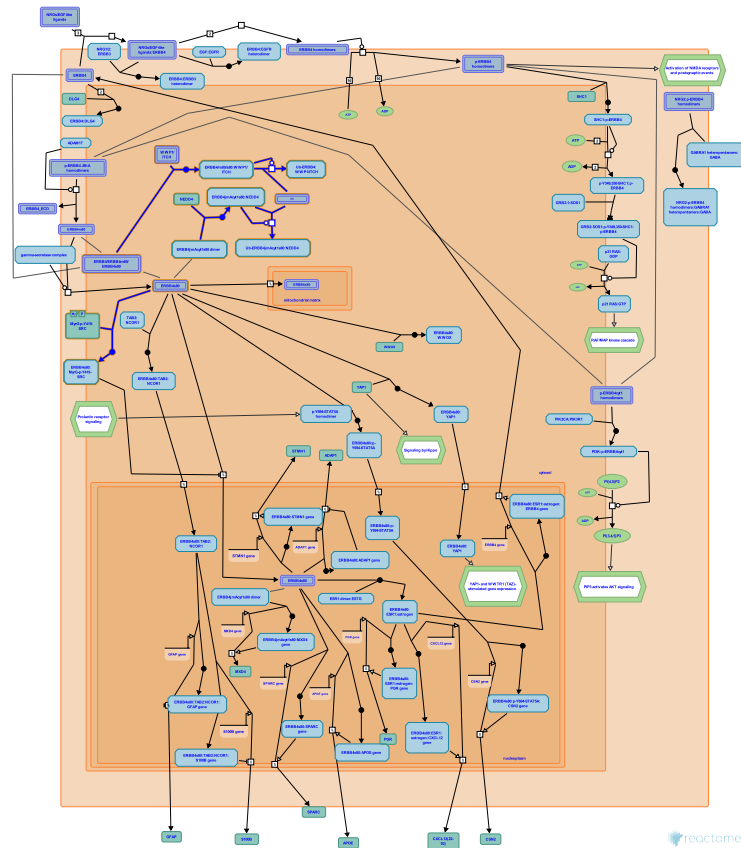

Earp HS, 3rd., Harris, RC., Matthews, L., Misior, AM., Orlic-Milacic, M., Stern, DF., Zeng, F.

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.

01/05/2024

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 1 pathway and 5 reactions (see Table of Contents)

Downregulation of ERBB4 signaling ↗

Stable identifier: R-HSA-1253288
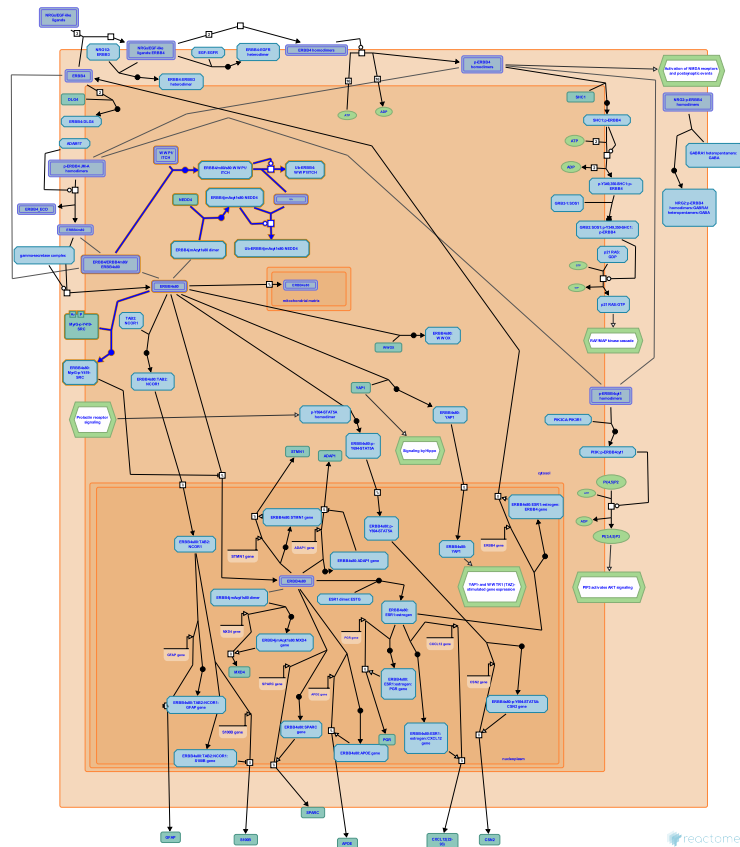
WW-domain binding motifs in the C-tail of ERBB4 play an important role in the downregulation of ERBB4 receptor signaling, enabling the interaction of intact ERBB4, ERBB4 m80 and ERBB4 s80 with NEDD4 family of E3 ubiquitin ligases WWP1 and ITCH. The interaction of WWP1 and ITCH with intact ERBB4 is independent 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).

Editions

|		
2011-11-04	Authored	Orlic-Milacic, M.
2011-11-07	Edited	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.

ERBB4 binds WWP1/ITCH ubiquitin ligases ↗

Location: Downregulation of ERBB4 signaling

Stable identifier: R-HSA-1253300

Type: binding

Compartments: plasma membrane, cytosol
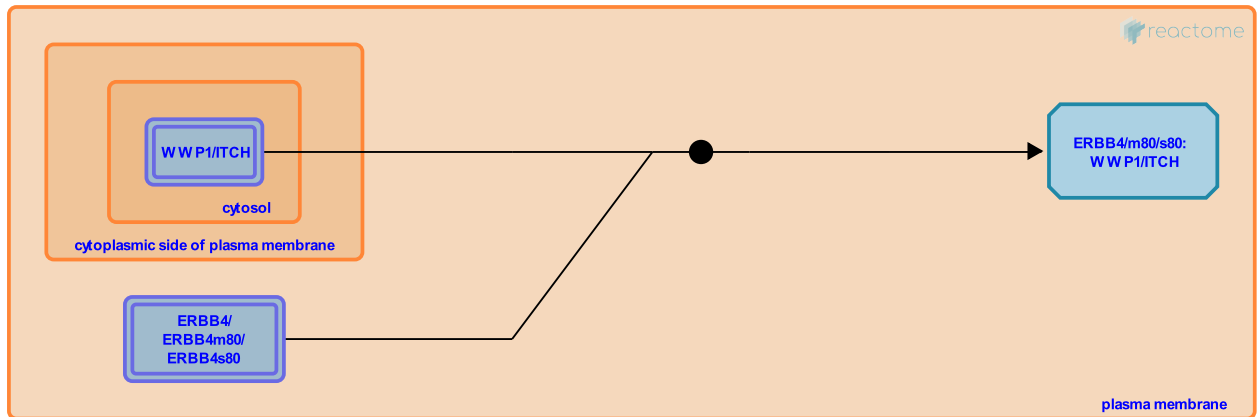
Intact ERBB4 isoforms and their membrane bound and cytosolic cleavage products, m80 and s80, bind NEDD4 family E3 ubiquitin ligases WWP1 and ITCH through WW-binding motifs in the C-tail. This interaction is independent of ligand binding and ERBB4 phosphorylation. CYT1 isoforms of ERBB4 have three WW-binding motifs: PY1, PY2 and PY3. PY2 motif is unique to CYT1 isoforms and overlaps with the PIK3R1 binding site. CYT2 isoform of ERBB4 has two WW-binding motifs: PY1 and PY3. While both CYT1 and CYT2 isoforms of ERBB4 all bind WWP1, CYT1 intracellular domain exhibits higher affinity for WWP1. Based on co-immunoprecipitation experiments in which individual WW-binding motifs of ERBB4 were mutated, Feng et al. established that PY2 had the highest affinity for WWP1, followed by PY3, while PY1 showed the lowest affinity (Omerovic et al. 2007, Feng et al. 2009).

Followed by: ERBB4 ubiquitination by WWP1/ITCH

Literature references

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. ↗

Marrocco, J., Torrisi, MR., Gulino, A., Di Marcotullio, L., Dall'Armi, C., Palumbo, C. et al. (2007). The E3 ligase Aip4/Itch ubiquitinates and targets ErbB-4 for degradation. *FASEB J, 21*, 2849-62. ↗

Editions

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

ERBB4 ubiquitination by WWP1/ITCH ↗

Location: Downregulation of ERBB4 signaling

Stable identifier: R-HSA-1253282

Type: transition

Compartments: plasma membrane, cytosol
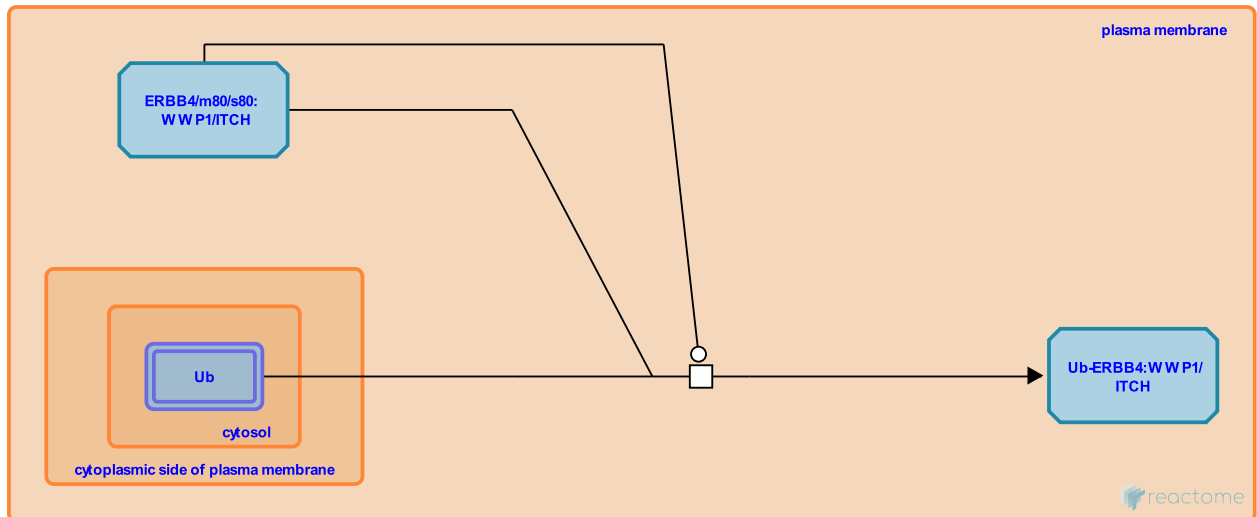
Upon binding to ERBB4 or its cleavage products m80 and s80, NEDD4 family ligases WWP1 and ITCH ubiquitinate intact and cleaved ERBB4 and target it for degradation (Omerovic et al. 2007, Feng et al. 2009).

Preceded by: ERBB4 binds WWP1/ITCH ubiquitin ligases

Literature references

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. ↗

Marrocco, J., Torrisi, MR., Gulino, A., Di Marcotullio, L., Dall'Armi, C., Palumbo, C. et al. (2007). The E3 ligase Aip4/Itch ubiquitinates and targets ErbB-4 for degradation. *FASEB J, 21*, 2849-62. ↗

Editions

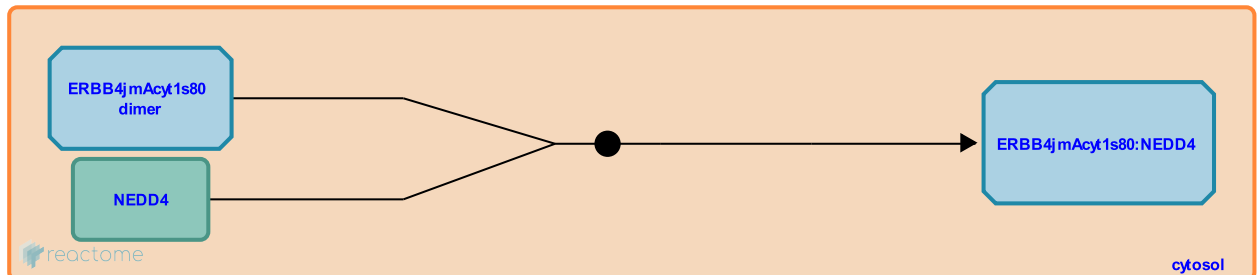|		
2011-11-04	Authored	Orlic-Milacic, M.
2011-11-07	Edited	Matthews, L.
2011-11-11	Reviewed	Harris, RC., Zeng, F.
2012-02-20	Reviewed	Earp HS, 3rd., Misior, AM.
2019-02-21	Authored	Stern, DF.
2019-03-06	Edited	Orlic-Milacic, M.

NEDD4 binds ERBB4jmAcyt1s80 dimer ↗

Location: Downregulation of ERBB4 signaling

Stable identifier: R-HSA-1973956

Type: binding

Compartments: cytosol

E3 ubiquitin ligase NEDD4 binds intracellular domain of ERBB4 isoform JM-A CYT1 (ERBB4jmAcyt1s80) produced by ERBB4 cleavage (Zeng et al. 2009).

Followed by: NEDD4 ubiquitinates ERBB4jmAcyt1s80 dimer

Literature references

Harris, RC., Zeng, F., Xu, J. (2009). Nedd4 mediates ErbB4 JM-a/CYT-1 ICD ubiquitination and degradation in MDCK II cells. *FASEB J, 23*, 1935-45. ↗

Editions

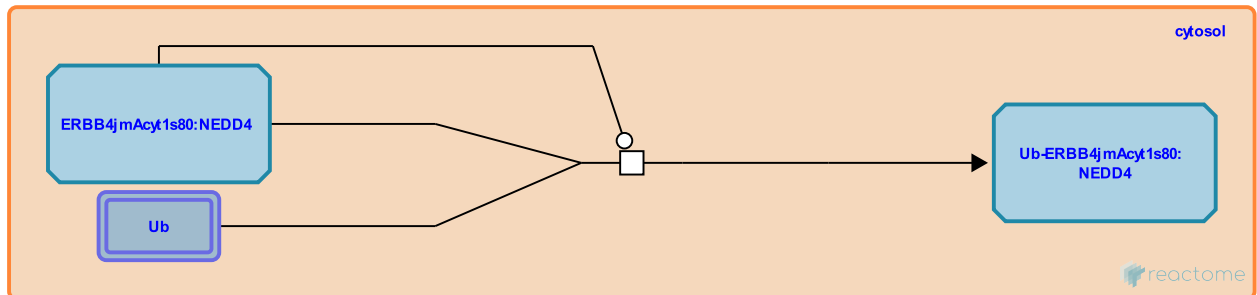|		
2011-11-04	Authored	Orlic-Milacic, M.
2011-11-07	Edited	Matthews, L.
2011-11-11	Reviewed	Harris, RC., Zeng, F.
2019-02-21	Authored	Stern, DF.
2019-03-06	Edited	Orlic-Milacic, M.

NEDD4 ubiquitinates ERBB4jmAcyt1s80 dimer ↗

Location: Downregulation of ERBB4 signaling

Stable identifier: R-HSA-1977296

Type: transition

Compartments: cytosol

E3 ubiquitin ligase NEDD4 mediates ubiquitination of ERBB4 JM-A CYT-1 intracellular domain s80 (ERBB4jmAcyt1s80) produced by ERBB4 cleavage. This induces degradation of ERBB4jmAcyt1s80, and decreases the amount of ERBB4jmAcyt1s80 that reaches the nucleus (Zeng et al. 2009).

Preceded by: NEDD4 binds ERBB4jmAcyt1s80 dimer

Literature references

Harris, RC., Zeng, F., Xu, J. (2009). Nedd4 mediates ErbB4 JM-a/CYT-1 ICD ubiquitination and degradation in MDCK II cells. *FASEB J, 23*, 1935-45. ↗

Editions

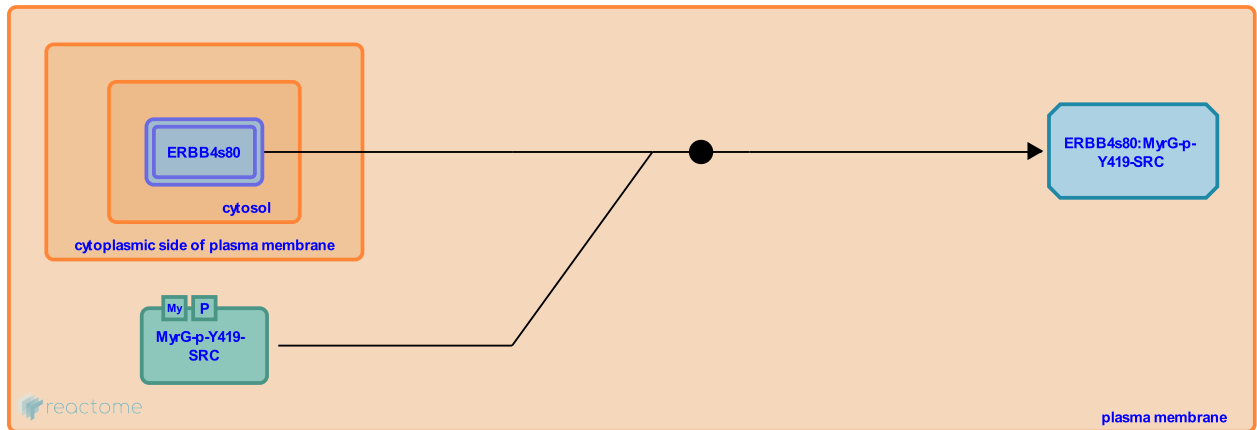|		
2011-11-04	Authored	Orlic-Milacic, M.
2011-11-07	Edited	Matthews, L.
2011-11-11	Reviewed	Harris, RC., Zeng, F.
2019-02-21	Authored	Stern, DF.
2019-03-06	Edited	Orlic-Milacic, M.

ERBB4s80 binds to SRC ↗

Location: Downregulation of ERBB4 signaling

Stable identifier: R-HSA-9612219

Type: binding

Compartments: plasma membrane, cytosol

SRC tyrosine kinase, activated by EGFR signaling, binds to the cleaved intracellular fragment of ERBB4, ERBB4s80 (E4ICD), released in response to ERBB4 activation by NRG1. Tyrosine phosphorylation of ERBB4s80 is needed for SRC binding. It is not clear whether tyrosine phosphorylation sites are auto-phosphorylated or phosphorylated by SRC. SRC binding prevents translocation of ERBB4s80 to the nucleus (Ishibashi et al. 2012).

Literature references

Kubota, S., Hasegawa, H., Ishibashi, K., Fukumoto, Y., Yamaguchi, N., Nakayama, Y. et al. (2013). Nuclear ErbB4 signaling through H3K9me3 is antagonized by EGFR-activated c-Src. *J. Cell. Sci., 126*, 625-37. ↗

Editions

2018-06-28	Authored	Orlic-Milacic, M.
2019-02-21	Authored	Stern, DF.
2019-03-06	Edited	Orlic-Milacic, M.

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