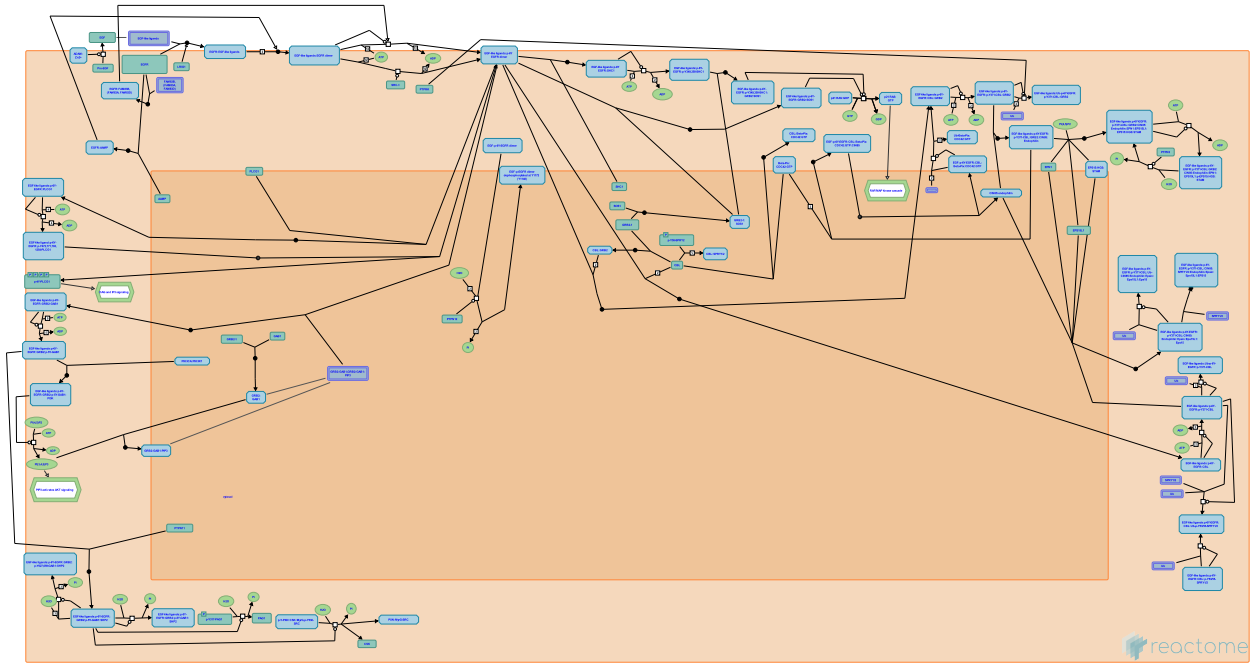
Signaling by EGFR



Castagnoli, L., Chen, GC., Heldin, CH., Hill, DP., Jassal, B., Kinsella, BT., Liu, X., Mulvaney, EP., Muthuswamy, S., Orlic-Milacic, M., Yao, S.

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.

03/05/2024

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.

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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. ↗

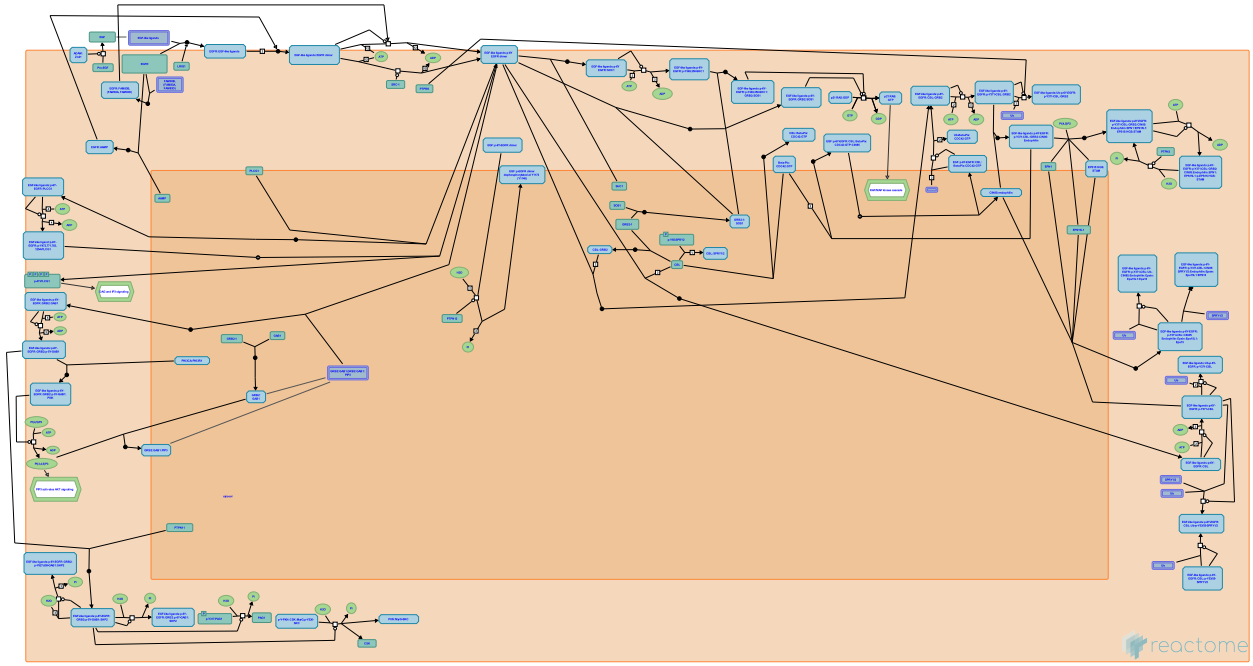
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Signaling by EGFR ↗

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.

Pro-EGF is cleaved to form mature EGF ↗

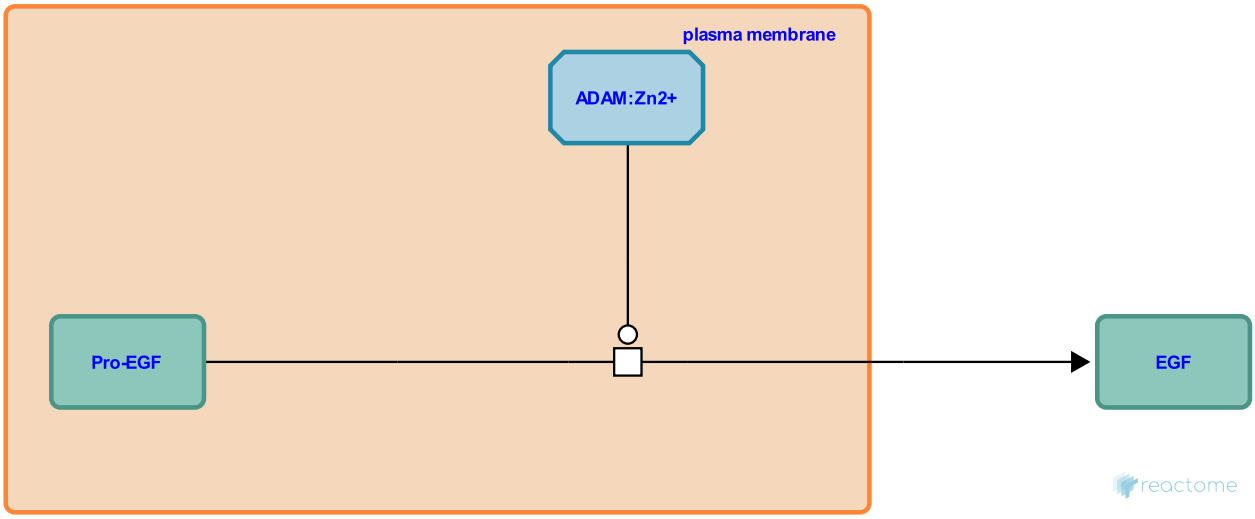
Location: Signaling by EGFR

Stable identifier: R-HSA-177946

Type: transition

Compartments: plasma membrane, extracellular region

Inferred from: Mouse pro-EGF is cleaved by ADAM sheddases (Mus musculus)



Ligands of the epidermal growth factor receptor (EGFR) are shed from the plasma membrane by metalloproteases. Identification of the sheddases for EGFR ligands using mouse embryonic cells lacking candidate sheddases (a disintegrin and metalloprotease; ADAM) has revealed that ADAM10, -12 and -17 are the sheddases of the EGFR ligands in response to various shedding stimulants such as GPCR agonists, growth factors, cytokines, osmotic stress, wounding and phorbol ester. Among the EGFR ligands, heparin-binding EGF-like growth factor (HB-EGF), EGF and TGF-alpha are the best characterized.

Followed by: EGFR binds EGF ligand

Editions

2006-10-10	Authored	Castagnoli, L.
2007-02-17	Reviewed	Muthuswamy, S.

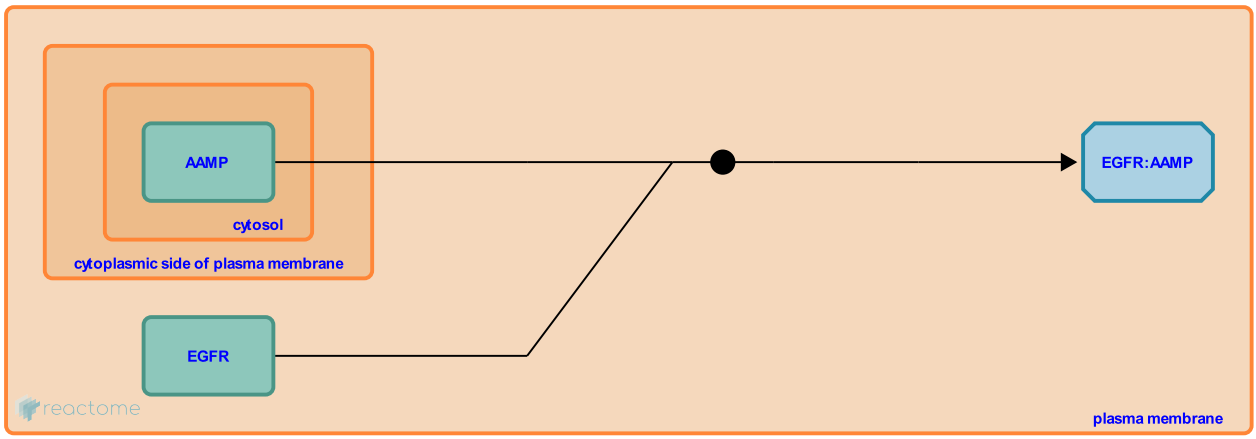
AAMP binds EGFR ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-9674531

Type: binding

Compartments: plasma membrane, cytoplasm



AAMP (Angio-associated migratory cell protein) binds to EGFR. The interaction involves the intracellular domain of EGFR. AAMP binding, through an unknown mechanism, promotes EGFR dimerization, trans-autophosphorylation and downstream signaling, leading to activation of ERKs (MAPK1 and MAPK3) and expression of cyclin D1 (CCND1). Downregulation of AAMP inhibits proliferation of a non-small cell lung cancer (NSCLC) cell line and increases its sensitivity to EGFR-targeted chemotherapeutic drugs, and it also inhibits tumorigenesis in a mouse model (Yao et al. 2019).
In addition to lung cancer, AAMP overexpression is linked with poor prognosis in breast cancer, where AAMP level positively correlates with tumor grade. AAMP is overexpressed in breast ductal carcinoma in situ (DCIS) with necrosis (Adeyinka et al. 2002).

Literature references

Sun, X., Zhang, Y., Yao, S., Sun, W., Su, L., Liu, X. et al. (2019). Angio-associated migratory cell protein interacts with epidermal growth factor receptor and enhances proliferation and drug resistance in human non-small cell lung cancer cells. *Cell. Signal., 61*, 10-19. ↗

Editions

2020-01-29	Authored	Orlic-Milacic, M.
2020-02-05	Reviewed	Liu, X., Yao, S.
2020-02-06	Reviewed	Kinsella, BT., Mulvaney, EP.
2020-02-10	Edited	Orlic-Milacic, M.
2023-10-30	Edited	Orlic-Milacic, M.

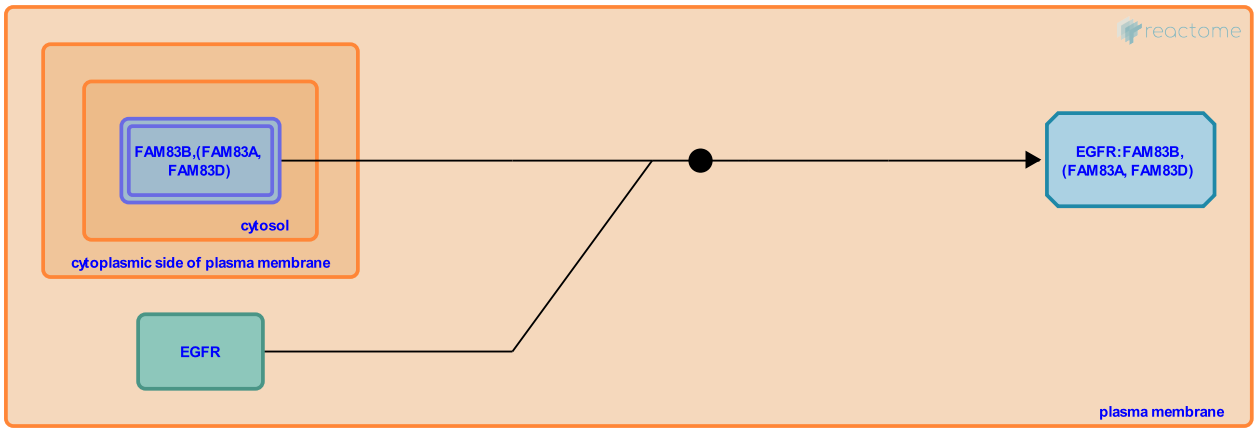
FAM83B, (FAM83A, FAM83D) bind EGFR ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-9851407

Type: binding

Compartments: plasma membrane, cytosol



Both recombinant and endogenous EGFR and FAM83B form a complex. The lysine residue K230 of FAM83B, conserved in other FAM83 family members, including FAM83A and FAM83D, is needed for binding to EGFR and stimulation of EGFR signaling. Through a mechanism that has not been elucidated, FAM83B stimulates basal and EGF-induced EGFR trans-autophosphorylation but dissociates from autophosphorylated EGFR (Cipriano et al. 2014).

FAM83B overexpression stimulates activation of MAPK and mTOR signaling downstream of EGFR, and prolongs activating EGFR, AKT and MAPK phosphorylation, increasing resistance to EGFR-targeting tyrosine kinase inhibitors (TKIs) AG1478, erlotinib, and CL387785 (Cipriano et al. 2012).

FAM83A overexpression similarly increases resistance of EGFR to EGFR-targeting TKIs AG1478, lapatinib, and gefitinib. In EGF-treated cells, tyrosine phosphorylation of FAM83A is increased, plausibly directly by EGFR, but the physical interaction between FAM83A and EGFR has not been reported. Downstream of EGFR activation, FAM83A associates with CRAF and PIK3R1. EGF treatment is not needed for FAM83A to interact with CRAF and PIK3R1 when FAM83A is overexpressed (Lee et al. 2012).

FAM83A-AS1 lncRNA, which is known to increase FAM83A expression, positively regulates EGFR signaling (Zhao et al. 2022).

FAM83D is highly expressed in invasive epithelial ovarian cancer. FAM83D-overexpressing cells demonstrate increased tyrosine phosphorylation of EGFR, as well as increased activating phosphorylation of downstream effectors of EGFR such as CRAF, ERK1/2 (MAPK3/1), and AKT (Zhang et al. 2019), but the direct interaction of FAM83D and EGFR has not been reported.

FAM83A and FAM83D are annotated as candidate binding partners or EGFR.

Literature references

Scott, SA., Bruntz, RC., Bryson, BL., Miskimen, KL., Brown, HA., Jackson, MW. et al. (2014). Hyperactivation of EGFR and downstream effector phospholipase D1 by oncogenic FAM83B. *Oncogene, 33*, 3298-306. ↗

Editions

2023-10-25	Authored	Orlic-Milacic, M.
2023-11-06	Reviewed	Hill, DP.
2023-11-09	Edited	Orlic-Milacic, M.

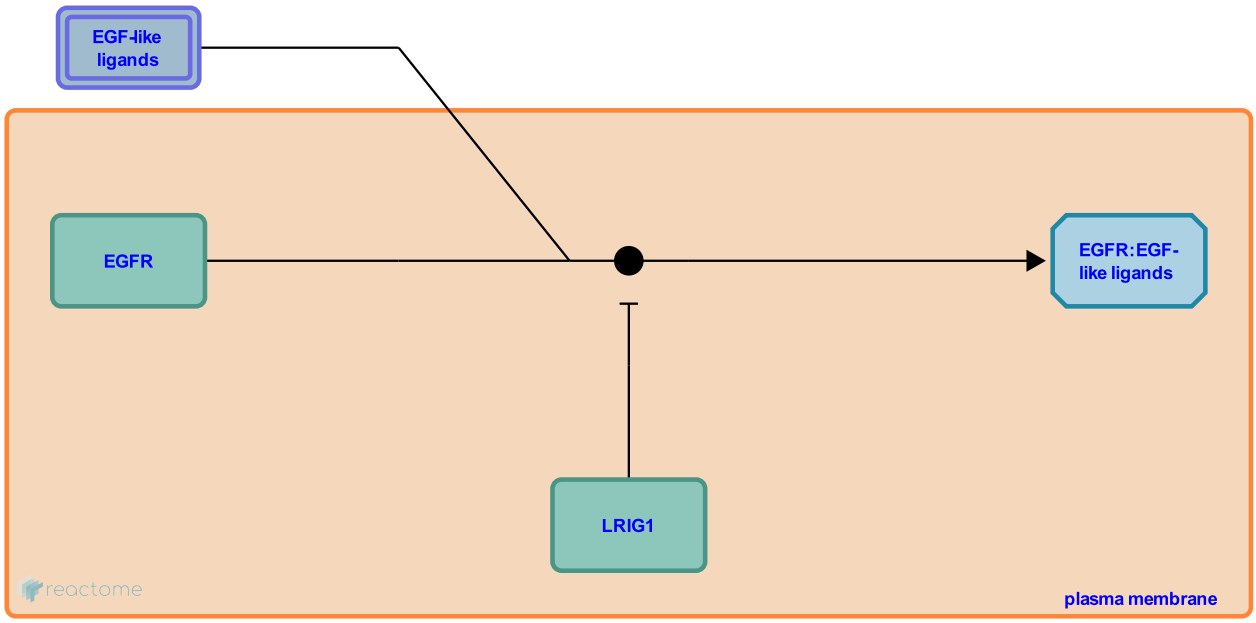
EGFR binds EGF ligand ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-177942

Type: binding

Compartments: plasma membrane, extracellular region



The prototypic receptor tyrosine kinase (RTK) EGFR is composed of 3 major domains; an extracellular domain linked via a single membrane-spanning domain to a cytoplasmic domain. EGF binds to the extracellular domain from where the signal is transmitted to the cytoplasmic domain.

Preceded by: Pro-EGF is cleaved to form mature EGF

Followed by: EGFR dimerization

Literature references

Kyte, J., Sherrill, JM. (1996). Activation of epidermal growth factor receptor by epidermal growth factor. *Biochemistry , 35*, 5705-18. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2007-02-17	Reviewed	Muthuswamy, S.

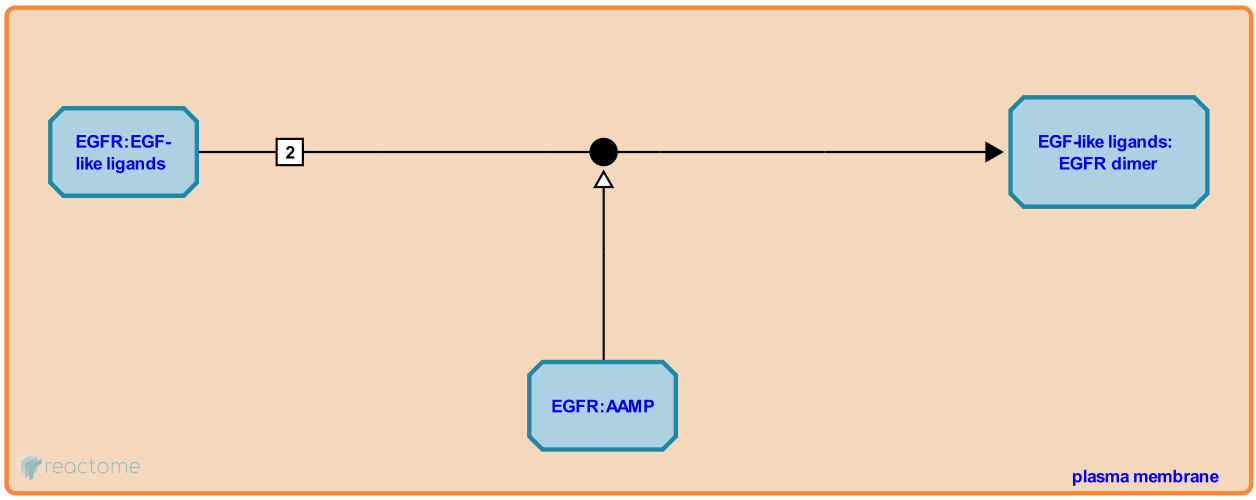
EGFR dimerization ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-177922

Type: binding

Compartments: plasma membrane, extracellular region



EGF and other growth factors induce oligomerization of their specific receptors. Inactive EGFR monomers are in equilibrium with active EGFR dimers and binding of the EGF ligand stabilizes the active dimeric form.

AAMP binding to EGFR, through an unknown mechanism, promotes EGFR dimerization, trans-autophosphorylation and downstream signaling, leading to activation of ERKs (MAPK1 and MAPK3) and expression of cyclin D1 (CCND1) (Yao et al. 2019). Positive regulation of EGFR dimerization by AAMP was shown in the context of EGF-mediated activation of EGFR signaling (Yao et al. 2019). The effect of AAMP in the context of other natural EGFR agonists (TGFA, AREG, EPGN, BTC, EREG, and HBEGF) has not been examined, but is assumed to be qualitatively similar.

Preceded by: EGFR binds EGF ligand

Followed by: Phosphorylation of EGFR by SRC kinase, EGFR autophosphorylation

Literature references

Kyte, J., Sherrill, JM. (1996). Activation of epidermal growth factor receptor by epidermal growth factor. *Biochemistry , 35*, 5705-18. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2007-02-17	Reviewed	Muthuswamy, S.
2023-10-25	Edited	Orlic-Milacic, M.
2023-11-02	Reviewed	Hill, DP.

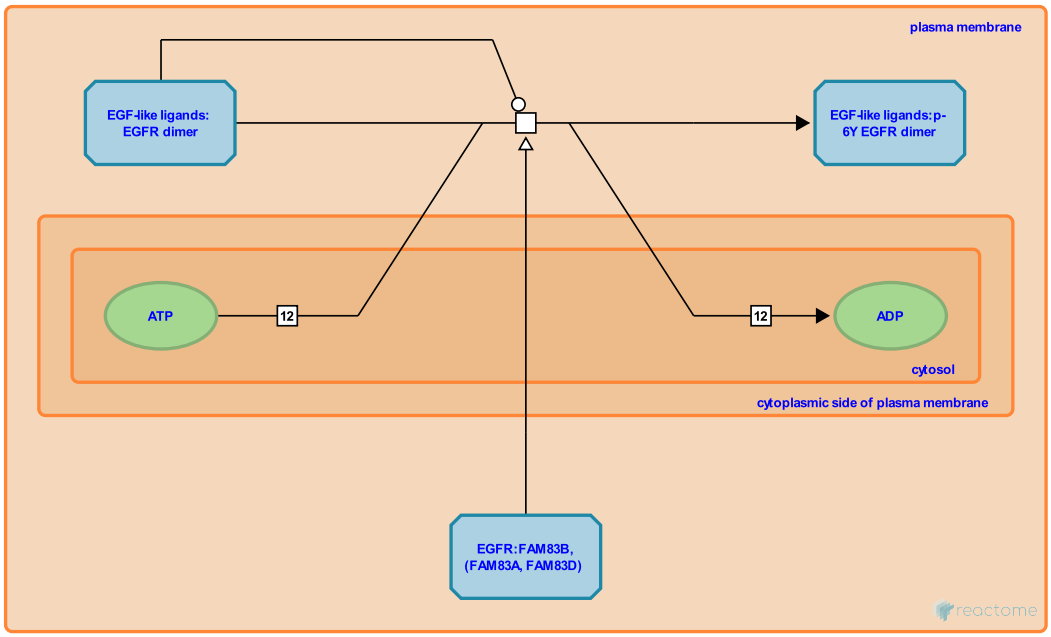
EGFR autophosphorylation ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-177934

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The cytoplasmic domain of EGFR contains tyrosine, serine and threonine phosphorylation sites. Dimerization of EGFR activates its intrinsic protein kinase activity and results in autophosphorylation of 6 tyrosine residues in the cytoplasmic tail of EGFR. Tyrosine autophosphorylation is crucial for normal receptor signaling. Five of these tyrosine residues (Y1016 i.e. Y992 in the mature protein, Y1092 i.e. Y1068 in the mature protein, Y1110 i.e. Y1086 in the mature protein, Y1172 i.e. Y1148 in the mature protein and Y1197 i.e. Y1173 in the mature protein) serve as specific binding sites for cytosolic target proteins involved in signal transmission, while the tyrosine residue Y1069 i.e. Y1045 in the mature protein is involved in recruitment of CBL ubiquitin ligase and downregulation of EGFR signaling through degradation of activated EGFR.

Binding of EGFR to FAM83B positively regulates both basal and EGF-induced trans-autophosphorylation of EGFR through an unknown mechanism. FAM83B is released from autophosphorylated EGFR (Cipriano et al. 2014). FAM83B positively regulates activation of AKT and MAPK signaling downstream of EGFR (Cipriano et al. 2012), consistent with its positive effect on EGFR trans-autophosphorylation. FAM83A positively regulates EGFR signaling, and may act as an EGFR effector as it is tyrosine phosphorylated upon EGFR activation and able to activate RAF and PI3K signaling (Lee et al. 2012). Direct binding of FAM83A to EGFR has not been reported, but the lysine residue K230 that is necessary for interaction of FAM83B with EGFR is conserved in FAM83A (Cipriano et al. 2014). FAM83A-AS1 lncRNA, known to increase FAM83A expression, positively regulates EGFR protein level (Zhao et al. 2022).

FAM83D, highly expressed in invasive epithelial ovarian cancer, positively regulates activating tyrosine phosphorylation of EGFR, as well as activating phosphorylation of EGFR downstream effectors CRAF, ERK1/2 (MAPK3/1), and AKT (Zhang et al. 2019). Direct binding of FAM83D to EGFR has not been reported, but the lysine residue K230 that is necessary for interaction of FAM83B with EGFR is conserved in FAM83D (Cipriano et al. 2014).

FAM83A and FAM83D are annotated as candidate binding partners or EGFR and as candidate positive regulators of EGFR trans-autophosphorylation.

Preceded by: EGFR dimerization

Literature references

Howk, R., Margolis, BL., Kris, R., Schlessinger, J., Givol, D., Honegger, AM. et al. (1989). All autophosphorylation sites of epidermal growth factor (EGF) receptor and HER2/neu are located in their carboxyl-terminal tails. Identification of a novel site in EGF receptor. *J Biol Chem, 264*, 10667-71.

Scott, SA., Bruntz, RC., Bryson, BL., Miskimen, KL., Brown, HA., Jackson, MW. et al. (2014). Hyperactivation of EGFR and downstream effector phospholipase D1 by oncogenic FAM83B. *Oncogene, 33*, 3298-306.

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.

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.

Editions

2006-10-10	Authored	Castagnoli, L.
2007-02-17	Reviewed	Muthuswamy, S.
2011-08-25	Edited	Orlic-Milacic, M.
2023-11-06	Reviewed	Hill, DP.

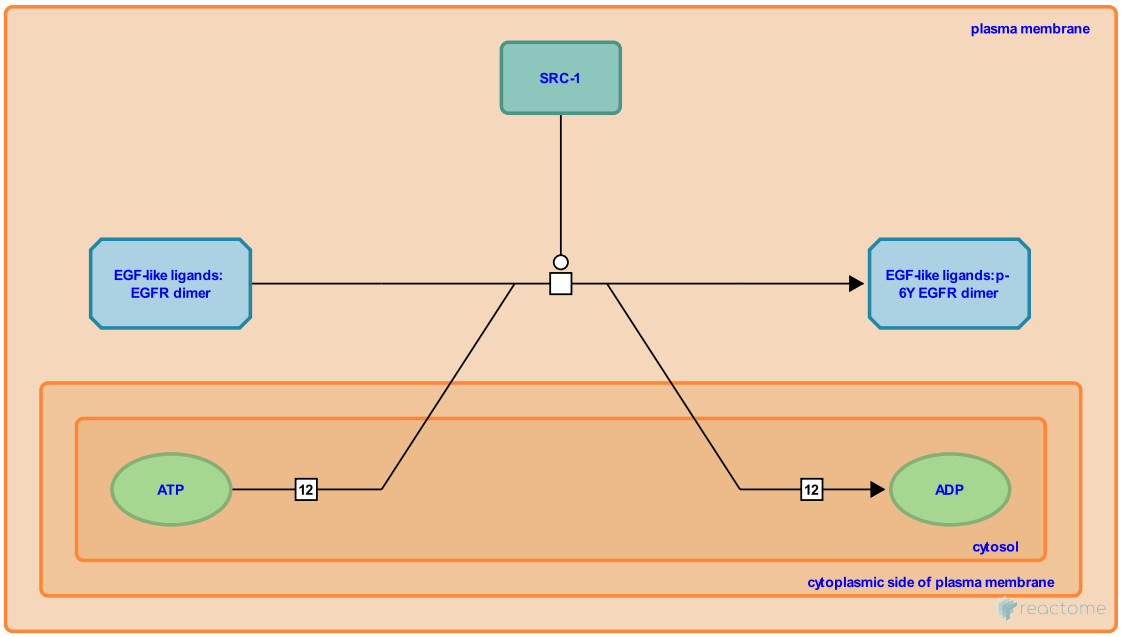
Phosphorylation of EGFR by SRC kinase ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-177937

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Besides autophosphorylation, EGFR can become tyrosine-phosphorylated by the action of the proto-oncogene tyrosine-protein kinase, c-src. This Src homology 2 (SH2) domain-containing protein is one of many such proteins which bind to phosphorylated sites on EGFR to affect signal transmission into the cell.

Preceded by: EGFR dimerization

Literature references

Lombardo, CR., Consler, TG., Kassel, DB. (1995). In vitro phosphorylation of the epidermal growth factor receptor autophosphorylation domain by c-src: identification of phosphorylation sites and c-src SH2 domain binding sites . *Biochemistry, 34*, 16456-66. ↗

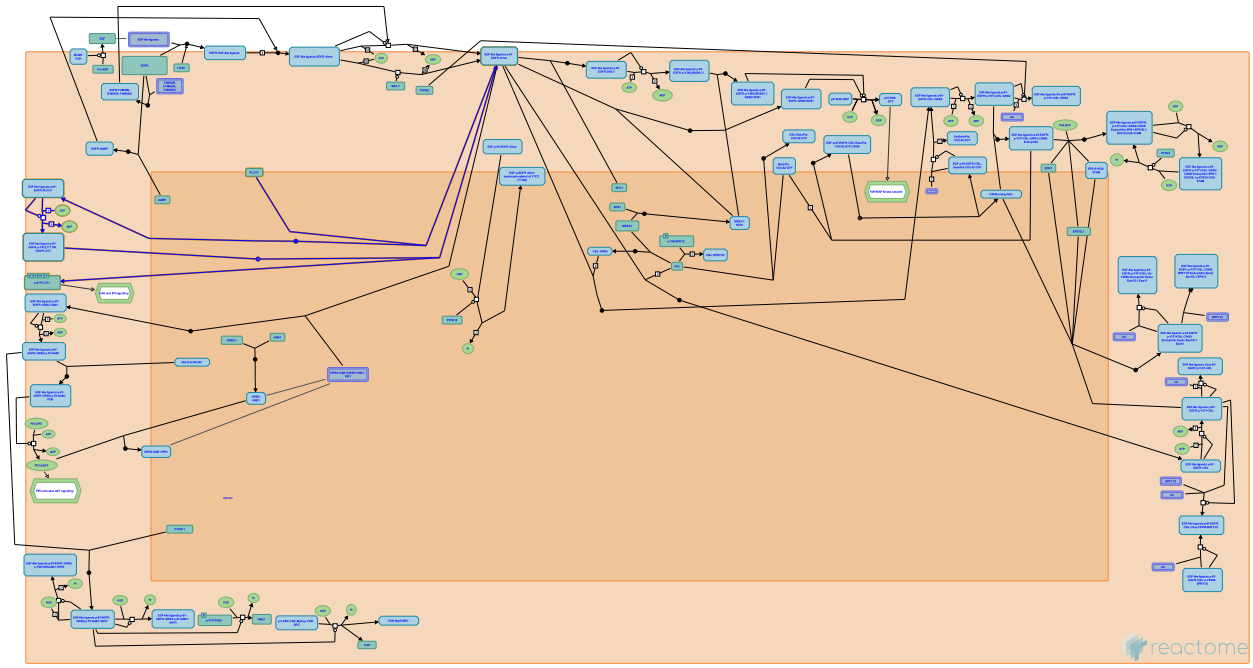
Editions

2006-10-10	Authored	Castagnoli, L.
2007-02-17	Reviewed	Muthuswamy, S.
2011-08-25	Edited	Orlic-Milacic, M.

EGFR interacts with phospholipase C-gamma ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-212718



Activated epidermal growth factor receptors (EGFR) can stimulate phosphatidylinositol (PI) turnover. Activated EGFR can activate phospholipase C-gamma1 (PLC-gamma1, i.e. PLCG1) which hydrolyses phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 is instrumental in the release of calcium from intracellular stores and DAG is involved in protein kinase C activation.

Literature references

Hernández-Sotomayor, SM., Carpenter, G. (1992). Epidermal growth factor receptor: elements of intracellular communication. *J Membr Biol, 128*, 81-9. ↗

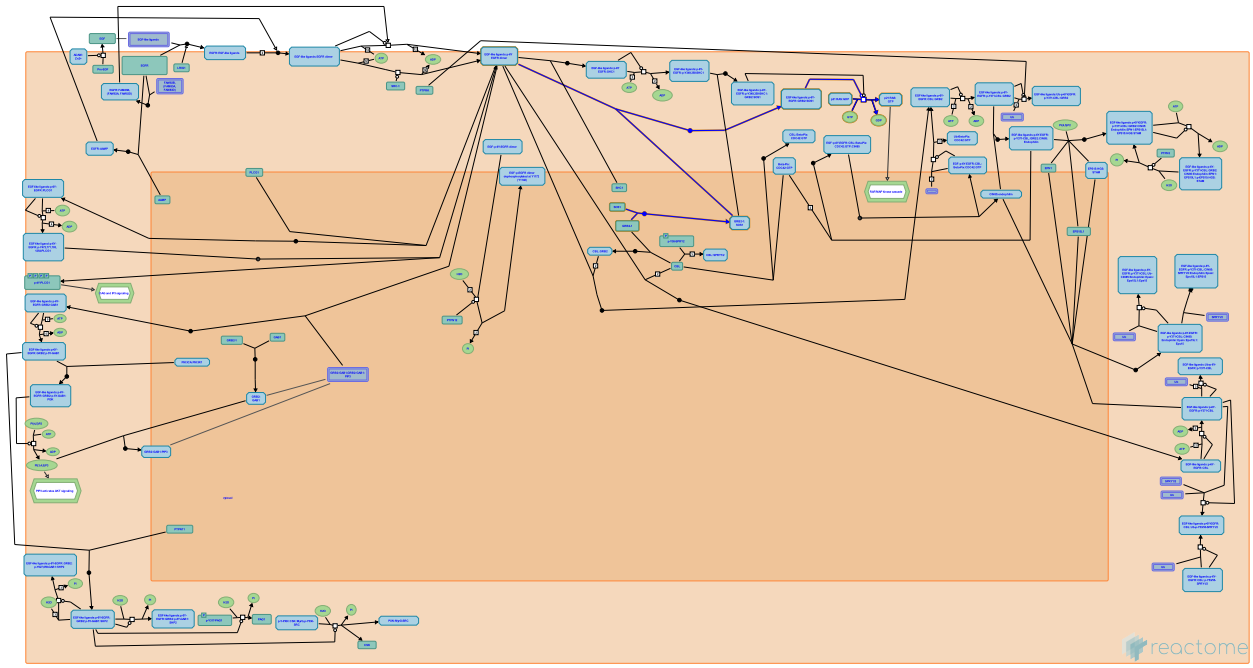
Editions

2008-02-12	Reviewed	Heldin, CH.
2008-02-13	Authored	Jassal, B.

GRB2 events in EGFR signaling ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-179812



Autophosphorylated EGFR tyrosine residues are docking sites for many downstream effectors in EGFR signaling. The adaptor protein GRB2 binds to phosphotyrosine residues in the C-tail of EGFR through its SH2 domain. GRB2 is constitutively associated with SOS, a guanine nucleotide exchange factor of RAS. GRB2 binding to phosphorylated EGFR results in the recruitment of SOS to the plasma membrane where it comes in proximity to RAS. This mechanism has been seen to be the model for RAS activation.

Literature references

Lopez-Berestein, G., Tari, AM. (2001). GRB2: a pivotal protein in signal transduction. *Semin Oncol, 28*, 142-7. ↗

Sorkin, A. (2001). Internalization of the epidermal growth factor receptor: role in signalling. *Biochem Soc Trans, 29*, 480-4. ↗

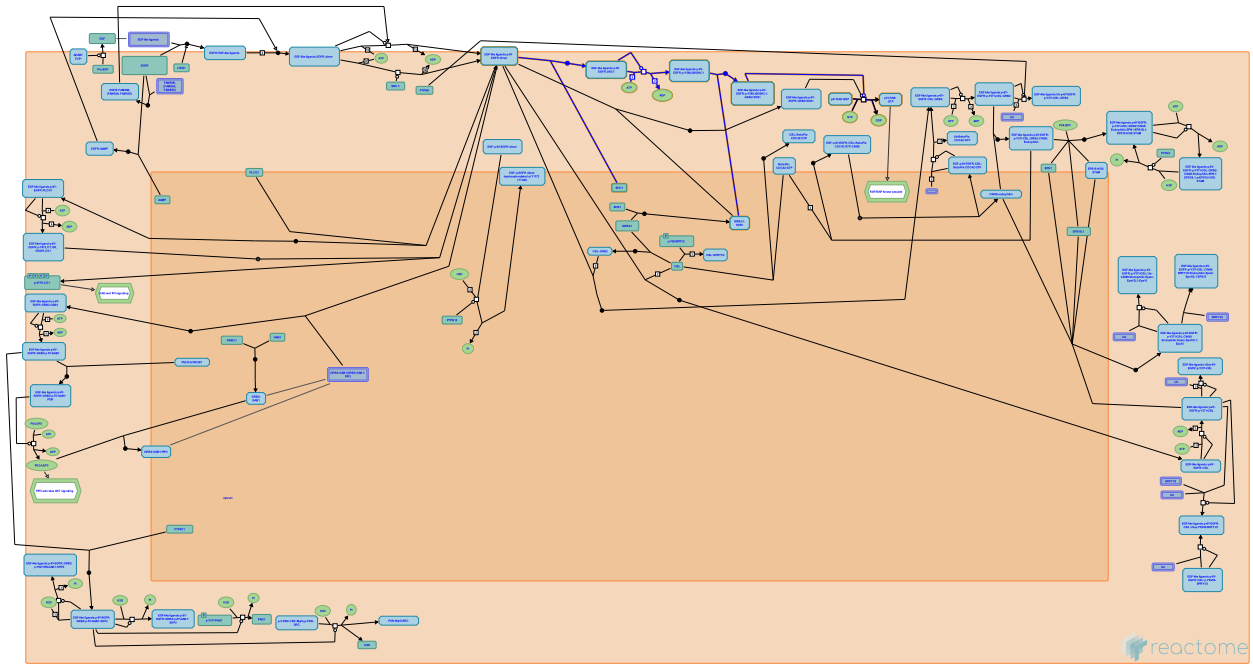
Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

SHC1 events in EGFR signaling ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-180336



GRB2 can bind EGFR directly or through another SH2-containing protein, SHC1. This association leads to RAS activation.

Literature references

Pelicci, G., Bonfini, L., Migliaccio, E., Lanfrancone, L., Pelicci, PG. (1996). Not all Shc's roads lead to Ras. *Trends Biochem Sci, 21*, 257-61. ↗

Sorkin, A. (2001). Internalization of the epidermal growth factor receptor: role in signalling. *Biochem Soc Trans, 29*, 480-4. ↗

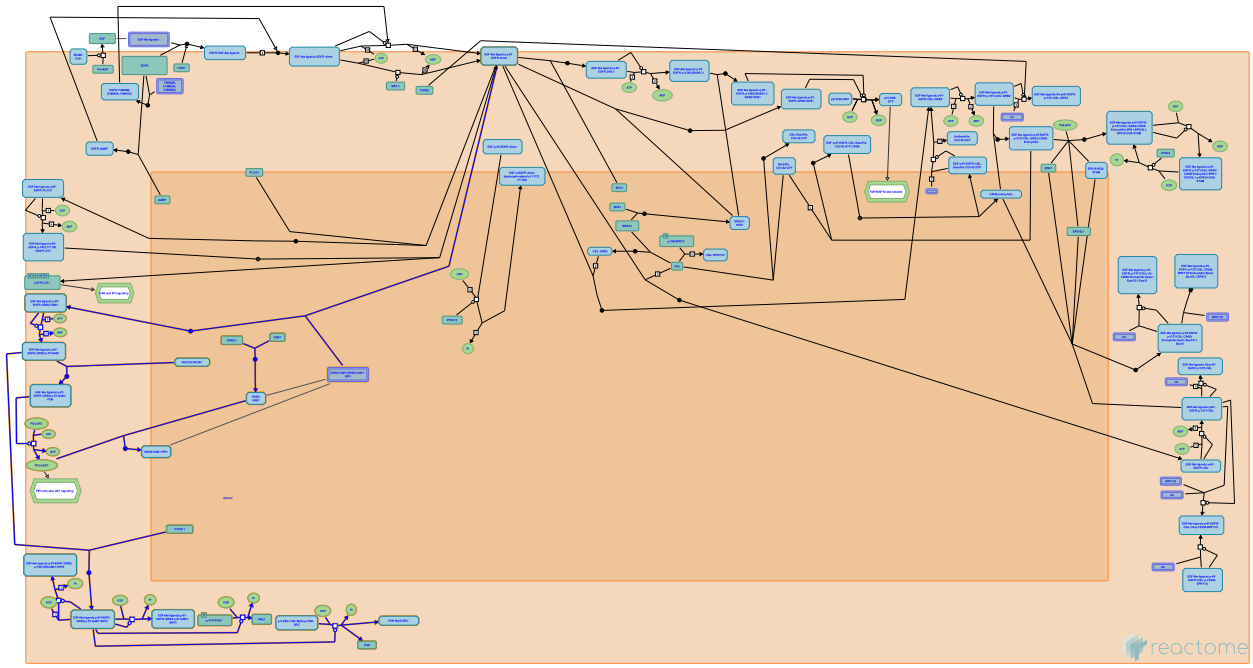
Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

GAB1 signalosome ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-180292



GAB1 is recruited to the activated EGFR indirectly, through GRB2. GAB1 acts as an adaptor protein that enables formation of an active PIK3, through recruitment of PIK3 regulatory subunit PIK3R1 (also known as PI3Kp85), which subsequently recruits PIK3 catalytic subunit PIK3CA (also known as PI3Kp110). PIK3, in complex with EGFR, GRB2 and GAB1, catalyzes phosphorylation of PIP2 and its conversion to PIP3, which leads to the activation of the AKT signaling.

Literature references

Schlessinger, J., Lax, I., Lamothe, B., Mattoon, DR. (2004). The docking protein Gab1 is the primary mediator of EGF-stimulated activation of the PI-3K/Akt cell survival pathway. *BMC Biol, 2*, 24. ↗

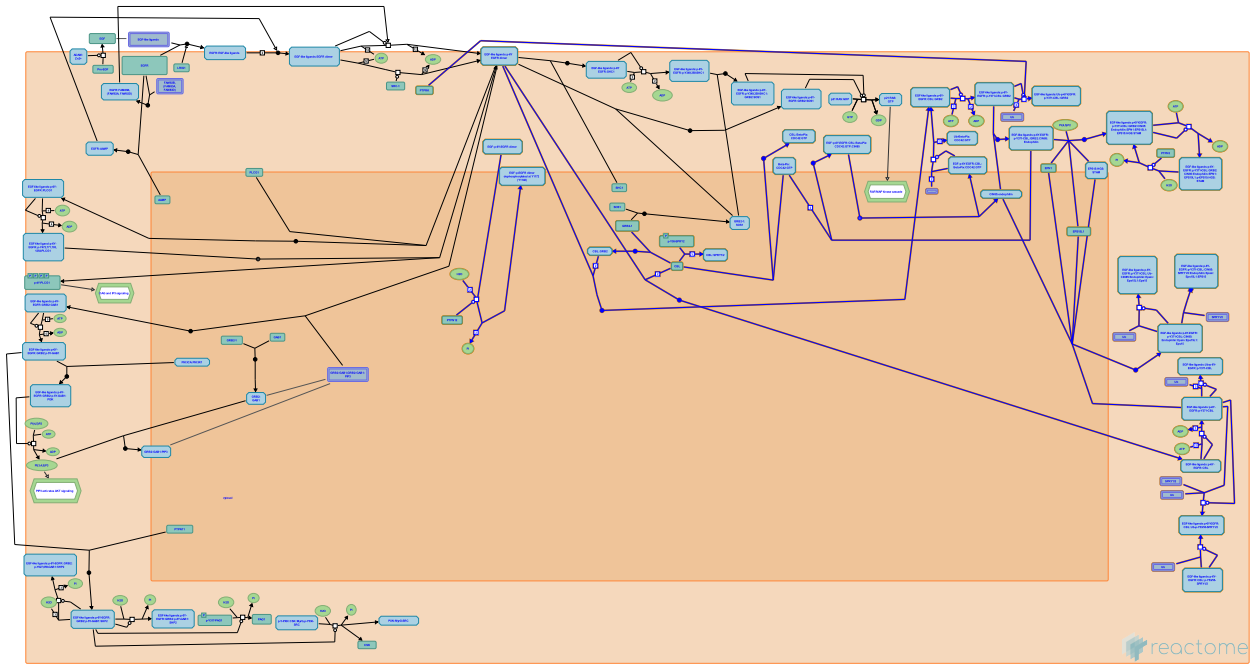
Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

EGFR downregulation ↗

Location: Signaling by EGFR

Stable identifier: R-HSA-182971



Regulation of receptor tyrosine kinase (RTK) activity is implicated in the control of almost all cellular functions. One of the best understood RTKs is epidermal growth factor receptor (EGFR). Growth factors can bind to EGFR and activate it to initiate signalling cascades within the cell. EGFRs can also be recruited to clathrin-coated pits which can be internalised into endocytic vesicles. From here, EGFRs can either be recycled back to the plasma membrane or directed to lysosomes for destruction.This provides a mechanism by which EGFR signalling is negatively regulated and controls the strength and duration of EGFR-induced signals. It also prevents EGFR hyperactivation as commonly seen in tumorigenesis.

The proto-oncogene Cbl can negatively regulate EGFR signalling. The Cbl family of RING-type ubiquitin ligases are able to poly-ubiquitinate EGFR, an essential step in EGFR degradation. All Cbl proteins have a unique domain that recognises phosphorylated tyrosine residues on activated EGFRs. They also direct the ubiquitination and degradation of activated EGFRs by recruiting ubiquitin-conjugation enzymes. Cbl proteins function by specifically targeting activated EGFRs and mediating their down-regulation, thus providing a means by which signaling processes can be negatively regulated.

Cbl also promotes receptor internalization via it's interaction with an adaptor protein, CIN85 (Cbl-interacting protein of 85kDa). CIN85 binds to Cbl via it's SH3 domain and is enhanced by the EGFR-induced tyrosine phosphorylation of Cbl. The proline-rich region of CIN85 interacts with endophilins which are regulatory components of clathrin-coated vesicles (CCVs). Endophilins bind to membranes and induce membrane curvature, in conjunction with other proteins involved in CCV formation. The rapid recruitment of endophilin to the activated receptor complex by CIN85 is the mechanism which controls receptor internalization.

Literature references

Langdon, WY., Thien, CB. (2001). Cbl: many adaptations to regulate protein tyrosine kinases. *Nat Rev Mol Cell Biol, 2*, 294-307. ↗

Dikic, I. (2003). Mechanisms controlling EGF receptor endocytosis and degradation. *Biochem Soc Trans, 31*, 1178-81. ↗

Marmor, MD., Yarden, Y. (2004). Role of protein ubiquitylation in regulating endocytosis of receptor tyrosine kinases . *Oncogene, 23*, 2057-70. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.
2016-05-06	Revised	Chen, GC.

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