EGFR downregulation

Ayoub, E., Castagnoli, L., Chen, GC., Heldin, CH., Jassal, B., Orlic-Milacic, M., Rothfels, K., Tremblay, M.
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


Reactome database release: 82

This document contains 1 pathway and 22 reactions (see Table of Contents)
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 its interaction with an adaptor protein, CIN85 (Cbl-interacting protein of 85kDa). CIN85 binds to Cbl via its 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**


## Editions

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Phosphorylation at tyrosine Y1045 of EGFR creates a major docking site for E3 ubiquitin-protein ligase, CBL (Casitas B-lineage lymphoma proto-oncogene) and is required to sort the EGFR to lysosomes for degradation. The E3 ligase CBL plays a crucial role in these events as it dually participates in early events of internalization via a CIN85-endophilin dependent mechanism and endocytic sorting by mediating multiple monoubiquitylation of the receptor.

Followed by: Phosphorylation of CBL (EGFR:CBL)

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Phosphorylation of CBL (EGFR:CBL)

Location: EGFR downregulation

Stable identifier: R-HSA-182969

Type: transition

Compartments: plasma membrane, cytosol

EGF (and indeed FGF, PDGF and NGF) stimulation results in CBL phosphorylation on Tyr-371. Phosphorylation is necessary for CBL to exhibit ubiquitin ligase activity.

Preceded by: Binding of CBL to EGFR

Followed by: Ubiquitination of stimulated EGFR (CBL), CBL binds and ubiquitinates phosphorylated Sprouty

Literature references


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Sprouty is ubiquitinated by CBL in an EGF-dependent manner. EGF stimulation induces the tyrosine phosphorylation of Sprouty, which in turn enhances the interaction of Sprouty with CBL. The CBL-mediated ubiquitination of Sprouty targets the protein for degradation by the 26S proteosome.

**Preceded by:** Phosphorylation of CBL (EGFR:CBL)

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Ubiquitination of stimulated EGFR (CBL)

Location: EGFR downregulation

Stable identifier: R-HSA-182993

Type: transition

Compartments: plasma membrane, cytosol

CBL down-regulates receptor tyrosine kinases by conjugating ubiquitin to them. This leads to receptor internalization and degradation. The ubiquitin protein ligase activity of CBL (abbreviated as E3 activity) is mediated by its RING finger domain. Receptor-type tyrosine-protein phosphatase kappa (PTPRK/RPT-Pk/DEP1) dephosphorylates EGFR, thereby inhibiting receptor ubiquitylation (Ub) by c-CBL, which decelerates the rate of receptor internalization and diminishes MAPK signals generated at the membrane and in endosomes. PTPRK disrupts physical association of ubiquitin ligase complex with EGFR and impairs its internalization (Tarcic et al. 2009, Xu et al. 2005).

Preceded by: Phosphorylation of CBL (EGFR:CBL)

Literature references


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https://reactome.org
CBL binds to GRB2

Location: EGFR downregulation

Stable identifier: R-HSA-183052

Type: binding

Compartments: cytosol

CBL binds multiple signalling proteins including GRB2. The CBL:GRB2 complex translocates to the plasma membrane where it can bind to GRB2-specific docking sites on the EGF receptor.

Followed by: Localization of CBL:GRB2 to the membrane

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Localization of CBL:GRB2 to the membrane

Location: EGFR downregulation

Stable identifier: R-HSA-183067

Type: binding

Compartments: plasma membrane, extracellular region, cytosol

Upon EGF stimulation and consequent EGFR phosphorylation, GRB2 binds phosphorylated tyrosines

Preceded by: CBL binds to GRB2

Followed by: Phosphorylation of CBL (EGFR:GRB2:CBL)

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Phosphorylation of CBL (EGFR:GRB2:CBL)

**Location:** EGFR downregulation

**Stable identifier:** R-HSA-183058

**Type:** transition

**Compartments:** plasma membrane, cytosol

EGF (and indeed FGF, PDGF and NGF) stimulation results in CBL phosphorylation on Tyr-371. Phosphorylation is necessary for CBL to exhibit ubiquitin ligase activity.

**Preceded by:** Localization of CBL:GRB2 to the membrane

**Followed by:** Ubiquitination of stimulated EGFR (CBL:GRB2)

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Ubiquitination of stimulated EGFR (CBL:GRB2)

**Location:** EGFR downregulation

**Stable identifier:** R-HSA-183036

**Type:** transition

**Compartments:** plasma membrane, cytosol

CBL down-regulates receptor tyrosine kinases by conjugating ubiquitin to them. This leads to receptor internalization and degradation. The ubiquitin protein ligase activity of CBL (abbreviated as E3 activity) is mediated by its RING finger domain. Receptor-type tyrosine-protein phosphatase kappa (PTPRK/RPT-Pk/DEP1) dephosphorylates EGFR, thereby inhibiting receptor ubiquitylation (Ub) by c-CBL, which decelerates the rate of receptor internalization and diminishes MAPK signals generated at the membrane and in endosomes. PTPRK disrupts physical association of ubiquitin ligase complex with EGFR and impairs its internalization (Tarcic et al. 2009, Xu et al. 2005).

**Preceded by:** Phosphorylation of CBL (EGFR:GRB2:CBL)

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Sprouty lures CBL away from EGFR

**Location:** EGFR downregulation

**Stable identifier:** R-HSA-182988

**Type:** omitted

**Compartments:** plasma membrane

The NEYTEG motif is very similar to the CBL binding motif around Tyr-1045 in EGFR. Tyrosine-phosphorylated Sprouty (hSpry) binds to CBL, which then cannot ubiquitinate EGFR. Sprouty acts as a decoy to lure CBL away from EGFR and targets it for degradation.

**Literature references**


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Activated CDC42 binds to Beta-Pix (p85Cool-1), a protein that directly associates with CBL. This inhibits the binding of CBL to the EGF receptor and thus prevents CBL from catalyzing receptor ubiquitination.

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Beta-Pix:CDC42:GTP binds CBL in EGF:p-6Y-EGFR:CBL:CIN85

Location: EGFR downregulation

Stable identifier: R-HSA-183002

Type: binding

Compartments: plasma membrane, cytosol

High concentrations of active CDC42 (bound to GTP) and Beta-Pix may promote the binding of Beta-Pix to CBL, pushing out the usually preferred binding partner CIN85 (SH3KBP1) from the CBL complex. This competitive mechanism could block the CIN85-imposed clustering phenomenon on CBL that is required for tighter binding (Schmidt et al. 2006).

Followed by: CIN85 dissociates from EGF:p-6Y-EGFR:CBL:Beta-Pix:CDC42:GTP:CIN85

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CIN85 dissociates from EGF:p-6Y-EGFR:CBL:Beta-Pix: CDC42:GTP:CIN85

Location: EGFR downregulation

Stable identifier: R-HSA-8951490

Type: dissociation

Compartments: plasma membrane, cytosol

High concentrations of active CDC42 (bound to GTP) and Beta-Pix may promote the binding of Beta-Pix to CBL, pushing out the usually preferred binding partner CIN85 (SH3KBP1) from the CBL complex. This competitive mechanism could block the CIN85-imposed clustering phenomenon on CBL that is required for tighter binding (Schmidt et al. 2006).

Preceded by: Beta-Pix:CDC42:GTP binds CBL in EGF:p-6Y-EGFR:CBL:CIN85

Followed by: CBL escapes CDC42-mediated inhibition by down-regulating the adaptor molecule Beta-Pix

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CBL escapes CDC42-mediated inhibition by down-regulating the adaptor molecule Beta-Pix

**Location:** EGFR downregulation

**Stable identifier:** R-HSA-183084

**Type:** transition

**Compartments:** plasma membrane, cytosol

Beta-Pix (Cool-1) associates with CBL, which appears to be a critical step in CDC42-mediated inhibition of EGFR ubiquitylation and downregulation. The SH3 domain of Beta-Pix specifically interacts with a proline-arginine motif (PxxxPR) present within CBL, which mediates ubiquitylation and subsequent degradation of Beta-Pix.

**Preceded by:** CIN85 dissociates from EGF:p-6Y-EGFR:CBL:Beta-Pix:CDC42:GTP:CIN85

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CBL-CIN85-Endophilin complex mediates ligand-induced down-regulation of the EGF receptor. The BAR domain of endophilin induces membrane curvature. The three SH3 domains of CIN85 bind to atypical proline-arginine motifs (PxxxPR) present in the carboxyl termini of CBL and CBL-b. In this way, CIN85 clusters CBL molecules, which is crucial for efficient EGFR endocytosis and degradation (Soubeyran et al. 2002).

Followed by: EGFR binds EPS15, EPN1, EPS15L1

Literature references

EGFR non-clathrin mediated endocytosis

Location: EGFR downregulation

Stable identifier: R-HSA-183072

Type: binding

Compartments: plasma membrane, cytosol

At higher concentrations of ligand, a substantial fraction of the receptor (>50%) is endocytosed through a clathrin independent, lipid-raft-dependent route as the receptor becomes Y1045 phosphorylated and ubiquitinated. Eps15 and Epsin are found in caveolae. Eps15 and Epsin are immunoprecipitated with the EGF receptor. Non-clathrin internalization of ubiquitinated EGFR depends on its interaction with proteins harbouring the UIM Ub-interacting motif, as shown through the ablation of three Ub-interacting motif-containing proteins, Eps15, Eps15R and Epsin.

Followed by: Sprouty sequesters CBL away from active EGFR, CBL-mediated ubiquitination of CIN85

Literature references


Sprouty is ubiquitinated by CBL in an EGF-dependent manner. EGF stimulation induces the tyrosine phosphorylation of Sprouty, which in turn enhances the interaction of Sprouty with CBL. The CBL-mediated ubiquitination of Sprouty targets the protein for degradation by the 26S proteasome.

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The adaptor protein CIN85 is monoubiquitinated by CBL after EGF stimulation. Monoubiquitination is thought to regulate receptor internalization and endosomal sorting.

**Preceded by:** EGFR non-clathrin mediated endocytosis

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Sprouty sequesters CBL away from active EGFR

**Location:** EGFR downregulation

**Stable identifier:** R-HSA-182990

**Type:** binding

**Compartments:** plasma membrane

Sprouty can constitutively interact with two SH3 domains of CIN85 whereas the third SH3 domain of CIN85 can still associate with CBL on cell activation with EGF. This allows Sprouty to block CIN85-mediated clustering of CBL molecules, stabilization of CBL-EGFR interactions and efficient ubiquitination and down-regulation of EGFR.

**Preceded by:** EGFR non-clathrin mediated endocytosis

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PTPN12 dephosphorylates EGFR at Y1148 (Y1172)

**Location:** EGFR downregulation

**Stable identifier:** R-HSA-8864029

**Type:** transition

**Compartments:** plasma membrane, cytosol

PTPN12 protein tyrosine phosphatase dephosphorylates activated EGFR at tyrosine residue Y1148 (Y1148 corresponds to Y1172 in the nascent EGFR sequence which includes the 24 amino acid long signal peptide at the N-terminus). PTPN12-mediated dephosphorylation of activated EGFR inhibits SHC1 recruitment to the p-Y1148 docking site, thus attenuating downstream RAS activation (Sun et al. 2011). The recruitment of SHC1 to p-Y1148 of EGFR is mediated by the N-terminal phosphotyrosine interaction domain (PID) of SHC1 (Batzner et al. 1995, Songyang et al. 1995).

**Literature references**


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**EGFR binds EPS15, EPN1, EPS15L1**

**Location:** EGFR downregulation

**Stable identifier:** R-HSA-8867044

**Type:** binding

**Compartments:** plasma membrane

EH-containing proteins such as EPS15, EPN1 and EPS15L1 are required for the endocytosis of ligand-activated EGFR (Confalonieri et al, 2000; Huang et al, 2004; reviewed in van Bergen en Henegouwen, 2009). EPS15 and EPN1 bind components of the clathrin coated pit through DPF motifs and likely bind to EGFR through the ubiquitin interacting motifs (UIMs). In this way EH proteins may help cluster activated EGFR into nascent clathrin-coated pits (Kazazic et al, 2009; Benmerah et al, 2000; reviewed in van Bergen en Henegouwen, 2009). Note, however, that EH-containing proteins are also involved in the clathrin-independent endocytosis of EGFR (Sigismund et al, 2005)

**Preceded by:** Assembly of EGFR complex in clathrin-coated vesicles

**Followed by:** EGFR phosphorylates EPS15

**Literature references**


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EGFR phosphorylates EPS15

Location: EGFR downregulation

Stable identifier: R-HSA-8867041

Type: transition

Compartments: plasma membrane

EPS15 is phosphorylated at Y849 by activated EGFR (Confalonieri et al, 2000). While the roles of phosphorylation and ubiquitination in EGFR endocytosis are unclear, emerging evidence suggests that EPS15 phosphorylation may target the activated EGFR complex for endocytosis through a clathrin-mediated route, while dephosphorylation at Y849 may direct the receptor complex into a clathrin-independent route (Confalonieri et al, 2002; de Melker et al, 2004; Li et al, 2015; reviewed in van Bergen en Hengouwen, 2009).

Preceded by: EGFR binds EPS15, EPN1, EPS15L1

Followed by: PTPN3 dephosphorylates EPS15

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PTPN3 dephosphorylates EPS15

Location: EGFR downregulation

Stable identifier: R-HSA-8867047

Type: transition

Compartments: plasma membrane

While the roles of EGFR and EPS15 phosphorylation and ubiquitination are not completely clear, recent evidence supports the idea that EGFR-mediated phosphorylation of EPS15 promotes the clustering of the activated receptor into clathrin-coated pits, while the dephosphorylated EPS15 targets EGFR for endocytosis through a caveolin-and lipid raft-dependent route (reviewed in van Bergen en Henegouwen, 2009). Consistent with this, overexpression of the phosphatase PTPN3, which dephosphorylates EPS15 in vitro and in vivo, promotes the internalization of EGFR into caveolin-enriched structures and targets it for lysosomal degradation (Li et al, 2015).

Preceded by: EGFR phosphorylates EPS15

Literature references


Editions

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