Signaling by EGFR

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16/03/2020
Introduction

Reactome is an 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: 71

This document contains 6 pathways and 5 reactions (see Table of Contents)
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 homodimerization 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 Y1045 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. For a recent review of EGFR signaling, please refer to Avraham and Yarden, 2011.

Literature references


**Editions**

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Pro-EGF is cleaved to form mature EGF

Location: Signaling by EGFR

Stable identifier: R-HSA-177946

Type: transition

Compartments: extracellular region, plasma membrane

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

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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**


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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.

Preceded by: EGFR binds EGF ligand

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

Literature references


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EGFR autophosphorylation

**Location:** Signaling by EGFR

**Stable identifier:** R-HSA-177934

**Type:** transition

**Compartments:** cytosol, plasma membrane, extracellular region

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 signalling. Five of these tyrosine residues (Y992, Y1068, Y1086, Y1148 and Y1173) serve as specific binding sites for cytosolic target proteins involved in signal transmission, while the tyrosine residue Y1045 is involved in recruitment of CBL ubiquitin ligase and downregulation of EGFR signaling through degradation of activated EGFR.

**Preceded by:** EGFR dimerization

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Phosphorylation of EGFR by SRC kinase

Location: Signaling by EGFR

Stable identifier: R-HSA-177937

Type: transition

Compartments: cytosol, plasma membrane, extracellular region

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


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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

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


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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.

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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.

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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.

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