EGFR downregulation

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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


Reactome database release: 79

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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Binding of CBL to EGFR

Location: EGFR downregulation

Stable identifier: R-HSA-183055