EPH-Ephrin signaling

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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.

17/11/2022

https://reactome.org
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 5 pathways and 6 reactions (see Table of Contents)
During the development process cell migration and adhesion are the main forces involved in morphing the cells into critical anatomical structures. The ability of a cell to migrate to its correct destination depends heavily on signaling at the cell membrane. Erythropoietin producing hepatocellular carcinoma (EPH) receptors and their ligands, the ephrins (EPH receptors interacting proteins, EFNs), orchestrates the precise control necessary to guide a cell to its destination. They are expressed in all tissues of a developing embryo and are involved in multiple developmental processes such as axon guidance, cardiovascular and skeletal development and tissue patterning. In addition, EPH receptors and EFNs are expressed in developing and mature synapses in the nervous system, where they may have a role in regulating synaptic plasticity and long-term potentiation. Activation of EPHB receptors in neurons induces the rapid formation and enlargement of dendritic spines, as well as rapid synapse maturation (Dalva et al. 2007). On the other hand, EPHA4 activation leads to dendritic spine elimination (Murai et al. 2003, Fu et al. 2007).

EPH receptors are the largest known family of receptor tyrosine kinases (RTKs), with fourteen total receptors divided into either A- or B-subclasses: EPHA (1-8 and 10) and EPHB (1-4 and 6). EPH receptors can have overlapping functions, and loss of one receptor can be partially compensated for by another EPH receptor that has similar expression pattern and ligand-binding specificities. EPH receptors have an N-terminal extracellular domain through which they bind to ephrin ligands, a short transmembrane domain, and an intracellular cytoplasmic signaling structure containing a canonical tyrosine kinase catalytic domain as well as other protein interaction sites. Ephrins are also sub-divided into an A-subclass (A1-A5), which are tethered to the plasma membrane by a glycosylphosphatidylinositol (GPI) anchor, and a B-subclass (B1-B3), members of which have a transmembrane domain and a short, highly conserved cytoplasmic tail lacking endogenous catalytic activity. The interaction between EPH receptors and its ligands requires cell-cell interaction since both molecules are membrane-bound. Close contact between EPH receptors and EFNs is required for signaling to occur. EPH/EFN-initiated signaling occurs bi-directionally into either EPH- or EFN-expressing cells or axons. Signaling into the EPH receptor-expressing cell is referred as the forward signal and signaling into the EFN-expressing cell, the reverse signal. (Dalva et al. 2000, Grunwald et al. 2004, Davy & Robbins 2000, Cowan et al. 2004)

**Literature references**


**Editions**

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EPHAs bind EFNAs

Location: EPH-Ephrin signaling

Stable identifier: R-HSA-3928646

Type: binding

Compartments: plasma membrane

The first step in the initiation of EPH-mediated signaling is the high affinity interaction between EPH receptors and ephrin (EFN) ligands of the same subclass located on closely opposed cell surfaces. Membrane bound EPHs bind to EFNs with high affinity and this results in the development of close contacts between the cells. This association between EPHs and EFNs on opposing cells is called trans-interaction and this close contact is required for signaling. This high affinity interaction usually result in contact-mediated repulsion. With some exceptions, the EPH receptor A-subclass (EPHA1-A8, A10) bind to the A-class ephrins (EFNA1-A4, A6). EPH and EFN initially form a 1:1 high affinity heterodimer, where ephrin inserts its extended loop into a channel at the surface of the receptor (Himanen et al. 2007, Himanen & Nikolov 2003, Himanen et al. 2001).

Followed by: EPH:EFN dimers tetramerise

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Followed by: EPH:EFN dimers tetramerise

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**EPH:EFN dimers tetramerise**

**Location:** EPH-Ephrin signaling

**Stable identifier:** R-HSA-3928597

**Type:** transition

**Compartments:** plasma membrane

Two class A or B EPH:EFN complexes dimerise to form a 2:2 tetramer, forming a ring-like structure, in which each receptor interacts with two ligands and each ligand with two receptors (Himanen et al. 2001). In the tetrameric form the molecules are arranged so that the C-termini of both ligands are located on one side, and the C-termini of the receptors on the other (Himanen & Nikolov 2003).

**Preceded by:** EPHAs bind EFNAs, EPHBs bind EFNBs

**Followed by:** EPH:EFN tetramers oligomerise

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The effective activation of the EPH kinase domain requires oligomerisation of EPH receptors and ephrins (EFNs) (Davis et al. 1994). Tetrameric EPH:EFN complexes aggregate into higher-ordered EPH:EFN clusters through several low-affinity EPH:EPH and EFN:EFN interactions, which may be responsible for EPH:EFN signaling (Stein et al. 1998, Pabbisetty et al. 2007).

**Preceded by:** EPH:EFN dimers tetramerise

**Followed by:** EPH receptors autophosphorylate

**Literature references**


Following ligand binding, EPH signaling is initiated through autophosphorylation. The cytoplasmic domain of EPH receptors can be divided into four functional units; the juxtamembrane region, a tyrosine kinase domain, a sterile alpha-motif (SAM) and a PDZ-domain binding motif. Multiple in vivo tyrosine phosphorylation sites were identified in the juxtamembrane region, kinase domain, and carboxy-terminal tail of EPH receptors. EPH receptors transduce forward signals into the cell through phosphorylation of these tyrosine (Y) residues. Two autophosphorylation sites within the juxtamembrane region (example phosphorylation sites being Y596 and 602 on EPHA4 and Y596 and 602 on EPHB2), and a Y residue within the kinase domain activation segment are identified as the key phosphorylation sites required for the catalytic activity of these EPH receptors. These Y residues are remarkably conserved between the EPHA and EPHB receptors. Substitution of these conserved Y residues in full-length EPHB2 leads to a reduction in ligand-induced kinase activity and EFN-stimulated tyrosine phosphorylation, suggesting that juxtamembrane Y residues may serve a regulatory function in addition to acting as docking sites for downstream targets. These autophosphorylated residues have been shown to interact with a number of proteins including Ras GTPase-activating protein (RasGAP), the p85 subunit of phosphatidylinositol 3-kinase, Src family kinases, the adapter protein NCK, and SHEP-1 (Binns et al. 2000).
**p-EPHs bind SRC,FYN,YES,LYN**

**Location**: EPH-Ephrin signaling

**Stable identifier**: R-HSA-3928584

**Type**: binding

**Compartments**: plasma membrane, cytosol

**Inferred from**: Interaction of Src family kinases with p-EPHs (Gallus gallus)

Src family kinases (SFKs) are one of the important components of EPH receptor-mediated axon guidance. Inhibition of SFK-mediated phosphorylation in retinal axons, abolishes EPHA-mediated repulsion in stripe and growth cone collapse assays (Knoll & Drescher 2004). Several members of the Src family, including SRC, FYN, LYN and YES, are expressed widely in the same places as EPH receptors. Autophosphorylated tyrosines in the juxtamembrane region of the EPH receptors have been shown to be critical for the association of the SRC and FYN SH2 domain (Ellis et al. 1996, Zisch et al. 1998). These SFKs are involved in the phosphorylation of RhoGEF ephexin1 and cortactin (Knoll & Drescher 2004). This event is deduced on the basis of experimental evidence from chicken assay studies (Knoll & Drescher 2004).

Specifically, activated EPHA4 was shown to form a complex with FYN and LYN kinases (Prevost et al. 2002).

**Preceded by**: EPH receptors autophosphorylate

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[https://reactome.org](https://reactome.org)
EPH-mediated growth cone collapse

**Location:** EPH-Ephrin signaling

**Stable identifier:** R-HSA-3928663

**Compartments:** plasma membrane, cytosol

EPH/Ephrin signaling is coupled to Rho family GTPases such as Rac, Rho and Cdc42 that connect bidirectional receptor-ligand interactions to changes in the actin cytoskeleton (Noren & Pasquale 2004, Groeger & Nobes 2007). RHOA regulates actin dynamics and is involved in EPHA-induced growth cone collapse. This is mediated by ephexins. Ephexin, a guanine nucleotide exchange factor for Rho GTPases, interacts with the EPHA kinase domain and its subsequent activation differentially affects Rho GTPases, such that RHOA is activated, whereas Cdc42 and Rac1 are inhibited. Activation of RHOA, and inhibition of Cdc42 and Rac, shifts actin cytoskeleton to increased contraction and reduced expansion leading to growth-cone collapse (Shamah et al. 2001, Sahin et al. 2005). The activation of EPH receptors in growing neurons typically, but not always, leads to a growth cone collapse response and retraction from an ephrin-expressing substrate (Poliakov et al. 2004, Pasquale 2005). EPHA-mediated repulsive responses prevent axons from growing into regions of excessive ephrin-A concentration, such as the posterior end of the superior colliculus (Pasquale 2005).

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Multiple EPHB receptors contribute directly to dendritic spine development and morphogenesis. These are more broadly involved in post-synaptic development through activation of focal adhesion kinase (FAK) and Rho family GTPases and their GEFs. Dendritic spine morphogenesis is a vital part of the process of synapse formation and maturation during CNS development. Dendritic spine morphogenesis is characterized by filopodia shortening followed by the formation of mature mushroom-shaped spines (Moeller et al. 2006). EPHBs control neuronal morphology and motility by modulation of the actin cytoskeleton. EPHBs control dendritic filopodia motility, enabling synapse formation. EPHBs exert these effects through interacting with the guanine exchange factors (GEFs) such as intersectin and kalirin. The intersectin-CDC42-WASP-actin and kalirin-RAC-PAK-actin pathways have been proposed to regulate the EPHB receptor mediated morphogenesis and maturation of dendritic spines in cultured hippocampal and cortical neurons (Irie & Yamaguchi 2002, Penzes et al. 2003). EPHBs are also involved in the regulation of dendritic spine morphology through FAK which activates the RHOA-ROCK-LIMK-1 pathway to suppress cofilin activity and inhibit cofilin-mediated dendritic spine remodeling (Shi et al. 2009).

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The interaction between ephrin (EFN) ligands and EPH receptors results not only in forward signaling through the EPH receptor, but also in 'reverse' signaling through the EFN ligand itself. Reverse signaling through EFNB is required for correct spine morphogenesis and proper path-finding of corpus callosum and dorsal retinal axons. The molecular mechanism by which EFNBs transduce a reverse signal involves phosphorylation of multiple, conserved tyrosines on the intracellular domain of B-type ephrins, facilitating binding of the SH2/SH3 domain adaptor protein GRB4 and subsequent cytoskeletal remodeling (Bruckner et al. 1997, Cowan & Henkemeyer 2001, Lu et al. 2001). The other mechanism of reverse signaling involves the C-terminus PSD-95/Dlg/ZO-1 (PDZ)-binding motif of EFNBs which recruits various PDZ domain containing proteins. Phosphorylation and PDZ-dependent reverse signaling by ephrin-B1 have each been proposed to play important roles in multiple contexts in development and disease (Bush & Soriano 2009).

Literature references

Despite high-affinity multimeric interaction between EPHs and ephrins (EFNs), the cellular response to EPH-EFN engagement is usually repulsion between the two cells and signal termination. These repulsive responses induce an EPH receptor-expressing cell to retract from an ephrin-expressing cell after establishing initial contact. The repulsive responses mediated by EPH receptors in the growth cone at the leading edge of extending axons and in axonal collateral branches contribute to the formation of selective neuronal connections. It is unclear how high affinity trans-cellular interactions between EPHs and ephrins are broken to convert adhesion into repulsion. Two possible mechanisms have been proposed for the repulsion of EPH-EFN bearing cells: the first one involves regulated cleavage of ephrin ligands or EPH receptors by transmembrane proteases following cell-cell contact, while the second one is rapid endocytosis of whole EPH:EFN complexes during the retraction of the interacting cells or neuronal growth cones (Egea & Klein 2007, Janes et al. 2005). RAC also plays an essential role during growth cone collapse by promoting actin polymerization that drives membrane internalization by endocytosis (Marston et al. 2003).

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EPHB-mediated forward signaling

Ephrin signaling

EPH-ephrin mediated repulsion of cells