

# Eph

## Key References

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## Overview

Members of the Eph receptor tyrosine kinase (RTK) family function as receptors and ligands for membrane-anchored ephrins. The Eph/ephrin system thus has the capacity to transduce signals into both the Eph- and ephrin-expressing cells. The Eph ectodomain is comprised of an N-terminal ephrin-binding domain, a cysteine-rich EGF-like domain and two membrane-proximal fibronectin type-III motifs. A single-pass hydrophobic transmembrane domain anchors Eph receptors in the plasma membrane and is contiguous with a cytoplasmic tail containing a regulatory juxtamembrane domain, a protein tyrosine kinase domain, a sterile  $\alpha$  motif and a PDZ domain-binding C-terminal tail. Two Eph receptor subclasses (A and B) are defined on the basis of binding preferences for ephrin ligands. EphA receptors preferentially bind glycosylphosphatidylinositol (GPI)-anchored A-subclass ephrins, and EphB receptors preferentially bind transmembrane B-subclass ephrins. However, some inter-subclass binding events are significant, such as EphA4/ephrinB2 and ephrinB3, and EphB2/ephrinA5.

EphB2 clustering is initiated by dimeric ephrinB2 binding to a high affinity site to form a 2:2 complex. This tetrameric complex is recruited to ring-like structures via a low affinity interface whereby one ephrin binds two Eph receptors. EphB2 clustering relieves catalytic autoinhibition through transphosphorylation of two tyrosine residues in the cytoplasmic juxtamembrane sequence, simultaneously creating docking sites for SH2 domain-containing proteins. Further Eph receptor autophosphorylation, and phosphorylation of recruited substrates, on tyrosine residues initiates forward signaling. The recruitment of proteins containing PDZ domains to Eph

receptor C-termini is also believed to play a role in the transduction of forward signals, but the regulation and *in vivo* significance of PDZ inter-actions remain poorly characterized. The activation of signal transduction into the ephrin-expressing cell is known as reverse signaling. While A-subclass ephrins can mediate reverse signaling, the mechanism is unknown. B-subclass ephrins share a conserved cytoplasmic tail and mediate reverse signaling via Src family kinase-dependent tyrosyl phosphorylation and the recruitment of adaptors such as Grb4. The C-termini of B-subclass ephrins also recruit proteins containing PDZ domains.

Eph/ephrin engagement at the cell surface signals bidirectionally to regulators of the actin cytoskeleton and cell-substrate adhesions to couple cell-cell contact with context-specific changes in motility and adhesion. While the more common outcome of Eph/ephrin engagement is unilateral or mutual cell de-adhesion or repulsion (e.g. restriction of cell intermingling at the interface of EphA4/ephrinB expression domains in adjacent rhombomeres), an adhesive response is generated under specific circumstances (e.g. in epithelial fusion during septation of the urinary and alimentary tracts mediated by EphB2/ephrinB2). Mechanisms which determine the cellular response to Eph/ephrin activation are complex and include ephrin ectodomain cleavage, endocytosis of Eph/ephrin complexes, extent of Eph/ephrin clustering, expression of truncated Eph receptor, Eph/ephrin engagement *in cis*, differential activation of signaling pathways and cell type-specific expression of signal transduction effectors. Crosstalk with other receptors and bidirectional signaling initiated by contact between cells which both coexpress Eph and ephrins may also play a role.

Although Eph receptors contribute to the regulation of many important embryonic developmental programs involving repulsive and attractive guidance (e.g. axon pathfinding), adhesive fusion and assembly (e.g. neural tube closure and angiogenesis, respectively), and cell segregation across interfaces and along gradients of Eph and ephrin expression (e.g. skeletogenesis and cell positioning in the intestinal epithelium, respectively), Eph receptors also function in the adult. In the vertebrate brain, Eph receptors regulate synaptic plasticity via forward and/or reverse signaling, with expression of Eph receptor observed on either the pre- or post-synaptic membrane in different circuits. Other roles involve a tumor suppressor function in the prostate and undefined pathological functions in the progression of other cancers.

# EphA

FAMILY MEMBERS	Eph A1	Eph A2	Eph A3
<b>OTHER NAMES</b>	EPHT, EPHT1, Esk	Eck, epithelial cell kinase, Myk2, Sek-2, Sek2	Chicken embryo kinase 4 (Cek4), ETK, ETK1, HEK4, human embryo kinase (HEK), Tyro4
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	108 kDa 976 aa	108.2 kDa 976 aa	110 kDa 983 aa
<b>ISOFORMS</b>	A1a, A1b	Not known	Truncated spliced variant
<b>SPECIES</b>	Human, mouse	Human, mouse	Human, mouse, rat, chicken
<b>DOMAIN ORGANIZATION</b>	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain
<b>PHOSPHORYLATION SITES</b>	Tyr <sup>599</sup> , Tyr <sup>605</sup> , Tyr <sup>781</sup> , Tyr <sup>930</sup>	Tyr <sup>588</sup> , Tyr <sup>594</sup> , Tyr <sup>772</sup> , Tyr <sup>921</sup>	Tyr <sup>596</sup> , Tyr <sup>602</sup> , Tyr <sup>779</sup>
<b>TISSUE DISTRIBUTION</b>	Placenta, overexpressed in several carcinomas	Epithelial	Placenta, widely expressed
<b>SUBCELLULAR LOCALIZATION</b>	Plasma membrane	Plasma membrane	Plasma membrane
<b>UPSTREAM ACTIVATORS</b>	A-subclass ephrins	A-subclass ephrins	A-subclass ephrins
<b>BINDING PARTNERS/ DOWNSTREAM ACTIVATION</b>	Pyk2, Ras, Rho	PI3K, Rac1, SLAP	Src, Fyn, Yes
<b>ACTIVATORS</b>	Not known	Not known	Not known
<b>INHIBITORS</b>	Not known	Not known	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Not known	Angiogenesis	Retinocollicular topographic mapping, axon pathfinding
<b>DISEASE RELEVANCE</b>	Not known	Tumor neovascularization, breast cancer, glioblastomas	Lung cancer

## FOOTNOTES

## EphA

FAMILY MEMBERS	Eph A4	Eph A5	Eph A6
<b>OTHER NAMES</b>	Cek8, chicken embryo kinase 8, Hek8, human embryo kinase 8, MPK-3, Pag, Pagliaccio, Rtk1, Rtk2, Rtk4, Sek, Sek1, TYRO1, Zek1, Zek2	Brain specific kinase (bsk), chicken embryo kinase 7 (Cek7), human embryo 7 (Hek7), Rek1	Ehk2, human embryo kinase 12 (Hek12)
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	109.8 kDa 986 aa	114.7 kDa 1037 aa	116.1 kDa 1035 aa
<b>ISOFORMS</b>	Not known	Not known	Not known
<b>SPECIES</b>	Human, mouse, chicken	Human, mouse, rat, chicken	Mouse, rat
<b>DOMAIN ORGANIZATION</b>	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain
<b>PHOSPHORYLATION SITES</b>	Tyr <sup>596</sup> , Tyr <sup>602</sup> , Tyr <sup>779</sup> , Tyr <sup>928</sup>	Tyr <sup>650</sup> , Tyr <sup>656</sup> , Tyr <sup>833</sup> , Tyr <sup>982</sup>	Tyr <sup>605</sup> , Tyr <sup>611</sup> , Tyr <sup>830</sup> , Tyr <sup>977</sup>
<b>TISSUE DISTRIBUTION</b>	Ubiquitous, brain, nervous system	Brain, nervous system	Nervous system, neurons
<b>SUBCELLULAR LOCALIZATION</b>	Plasma membrane	Plasma membrane	Plasma membrane
<b>UPSTREAM ACTIVATORS</b>	A-subclass ephrins, ephrin-B3	A-subclass ephrins	A-subclass ephrins
<b>BINDING PARTNERS/ DOWNSTREAM ACTIVATION</b>	Src, Fyn, Fes, Abl, PLCγ, RhoB, cdc42/Rac family of GTPases, Vav, ephexin	Not known	Not known
<b>ACTIVATORS</b>	Not known	Not known	Not known
<b>INHIBITORS</b>	Not known	Not known	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Axon pathfinding, synaptic plasticity, neural crest migration, hindbrain segmentation, somitogenesis, neuroblast migration and proliferation, platelet aggregation	Retinocollicular topographic mapping, vomero-nasal- accessory olfactory bulb topographic mapping, axon pathfinding, olfactory sensory neuronal topographic mapping, pathfinding	Retinocollicular topographic mapping, vomero-nasal- accessory olfactory bulb topographic mapping, axon pathfinding
<b>DISEASE RELEVANCE</b>	Sezary syndrome	Glioblastomas	Not known

## FOOTNOTES

# EphA

FAMILY MEMBERS	Eph A7	Eph A8	Eph A9	Eph A10
<b>OTHER NAMES</b>	Chicken embryo kinase 11 (cek11), Ebk, human embryo kinase 11 (Hek11), MDK-1, mouse developmental kinase 1 (Mdk1)	Eph and elk related tyrosine kinase (Eek), human embryo kinase 3 (HEK3)	Not known	Not known
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	112 kDa 998 aa	111 kDa 1005 aa	120-130 kDa 969 aa	295, 543 kDa 1008 aa
<b>ISOFORMS</b>	Truncated splice variant	Not known	Not known	EphA10s, EphA10*, EphA10
<b>SPECIES</b>	Human, mouse, rat, chicken	Human, mouse, rat, chicken	Chicken	Human
<b>DOMAIN ORGANIZATION</b>	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain
<b>PHOSPHORYLATION SITES</b>	Tyr <sup>608</sup> , Tyr <sup>614</sup> , Tyr <sup>791</sup> , Tyr <sup>940</sup>	Tyr <sup>616</sup> , Tyr <sup>839</sup>	Not known	Not known
<b>TISSUE DISTRIBUTION</b>	Ubiquitous	Brain	Kidney, lung, testis, thymus	Testis
<b>SUBCELLULAR LOCALIZATION</b>	Plasma membrane	Plasma membrane	Plasma membrane	Plasma membrane
<b>UPSTREAM ACTIVATORS</b>	A-subclass ephrins	A-subclass ephrins	A-subclass ephrins	A-subclass ephrins
<b>BINDING PARTNERS/ DOWNSTREAM ACTIVATION</b>	Not known	Fyn, MAPK, LMW-PTP, PI3K	Not known	Not known
<b>ACTIVATORS</b>	Not known	Not known	Not known	Not known
<b>INHIBITORS</b>	Not known	Not known	Not known	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Retinocollicular topographic mapping, vomero-nasal-accessory olfactory bulb topographic mapping, neural tube closure, axon pathfinding	Axon pathfinding	Not known	Not known
<b>DISEASE RELEVANCE</b>	Hepatocellular carcinomas	Colon carcinomas	Not known	Not known

## FOOTNOTES

# EphB

FAMILY MEMBERS	Eph B1	Eph B2	Eph B3
<b>OTHER NAMES</b>	Chicken embryo kinase 6 (Cek6), Elk, EPHT2, human embryo kinase 6 (HEK6), NET	Chicken embryo kinase 5 (Cek5), DRT, ELK-related protein kinase, EPHT3, ERK, ETECK, human embryo kinase 5 (HEK5), Nuk, Prkm5, Qek5, Sek3, Tyro5	Chicken embryo kinase 10 (Cek10), Etk2, HEK2, human embryo kinase 2, (HEK2), Mdk5, mouse developmental kinase 5, Sek4, Tyro6
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	109.9 kDa 984 aa	117.5 kDa 1055 aa	110.3 kDa 998 aa
<b>ISOFORMS</b>	Not known	Truncated splice variant	Not known
<b>SPECIES</b>	Human, rat, chicken, mouse	Human, mouse, chicken, rat	Human, mouse, chicken, zebrafish, rat, <i>Xenopus</i>
<b>DOMAIN ORGANIZATION</b>	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain
<b>PHOSPHORYLATION SITES</b>	Tyr <sup>594</sup> , Tyr <sup>600</sup> , Tyr <sup>778</sup> , Tyr <sup>928</sup>	Tyr <sup>596</sup> , Tyr <sup>602</sup> , Tyr <sup>605</sup> , Tyr <sup>611</sup> Tyr <sup>780</sup> , Tyr <sup>930</sup>	Tyr <sup>608</sup> , Tyr <sup>614</sup> , Tyr <sup>792</sup> , Tyr <sup>942</sup>
<b>TISSUE DISTRIBUTION</b>	Brain, kidney	Brain, heart, lung, kidney, placenta, pancreas, liver, skeletal muscle, nervous system	Ubiquitous
<b>SUBCELLULAR LOCALIZATION</b>	Plasma membrane	Plasma membrane	Plasma membrane
<b>UPSTREAM ACTIVATORS</b>	B-subclass ephrins	B-subclass ephrins, ephrin A-5	B-subclass ephrins
<b>BINDING PARTNERS/ DOWNSTREAM ACTIVATION</b>	Paxillin, NIK, integrins, JNK, LMW-PTP, Nck, Grb2, Grb10	Synj1, Sdc2, Abl, Src, Yes, RasGAP, Nck, PLCγ, LMW-PTP, AF6, Pick-1, GRIP, Kalirin, intersectin, NMDA receptor	RasGAP, Crk, AF6
<b>ACTIVATORS</b>	Not known	Not known	Not known
<b>INHIBITORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Hindbrain segmentation, skeletal development, axon pathfinding, angiogenesis, neural crest migration, dendritic spine development, neuroblast migration and proliferation, synaptic plasticity, platelet aggregation	Hindbrain segmentation, skeletal development, axon pathfinding, retinocollicular topographic mapping, angiogenesis, midline fusion/septation, synaptic plasticity, neural crest migration, vestibular function, dendritic spine development, cell positioning in intestinal epithelium, neuroblast migration and proliferation, endocytosis	Hindbrain segmentation, skeletal development, axon pathfinding, retinocollicular topographic mapping, angiogenesis, midline fusion/septation, neural crest migration, vestibular function, dendritic spine development, cell positioning in intestinal epithelium, neuroblast migration and proliferation, synaptic plasticity, endocytosis
<b>DISEASE RELEVANCE</b>	Not known	Tumor suppressor in prostate and colon, breast carcinomas, hepatocellular, domains	Colon carcinomas

## FOOTNOTES

# EphB

<b>FAMILY MEMBERS</b>	Eph B4	Eph B6
<b>OTHER NAMES</b>	Htk, mouse developmental kinase 2 (Mdk2), Myk1, Tyro11	HEP, Mep
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	108.2 kDa 987 aa	109.2 kDa 1006 aa
<b>ISOFORMS</b>	Not known	Truncated splice variant
<b>SPECIES</b>	Human, mouse	Human, mouse
<b>DOMAIN ORGANIZATION</b>	Ephrin binding domain, 2 fibronectin type-III domains, 1 protein tyrosine kinase domain, 1 SAM domain	Ephrin binding domain, 2 fibronectin type-III domains, 1 SAM domain, 1 inactive/dead protein tyrosine kinase domain
<b>PHOSPHORYLATION SITES</b>	Tyr <sup>590</sup> , Tyr <sup>596</sup> , Tyr <sup>774</sup> , Tyr <sup>924</sup>	Not known
<b>TISSUE DISTRIBUTION</b>	Placenta, fetal brain, venous endothelial cells	Brain, pancreas, thymus
<b>SUBCELLULAR LOCALIZATION</b>	Plasma membrane	Plasma membrane
<b>UPSTREAM ACTIVATORS</b>	B-subclass ephrins	B-subclass ephrins
<b>DOWNSTREAM ACTIVATION</b>	RasGAP, Src, PI3K	AF6, Fyn, Rac/JNK, TCR/MAPK
<b>ACTIVATORS</b>	Not known	Not known
<b>INHIBITORS</b>	Not known	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Angiogenesis	T cell regulation
<b>DISEASE RELEVANCE</b>	Tumor neovascularization, breast carcinomas, glioblastomas, prostate cancer	Neuroblastomas, metastatic melanoma

## FOOTNOTES